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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>G01N 33/68, 33/53, C07K 16/00, C12N 15/11, 15/12, 15/00, 15/63, A61K 38/17, 38/16, C12P 21/02</b>		<b>A1</b>	(11) International Publication Number: <b>WO 99/24836</b> (43) International Publication Date: <b>20 May 1999 (20.05.99)</b>																																										
(21) International Application Number: <b>PCT/US98/23435</b> (22) International Filing Date: <b>4 November 1998 (04.11.98)</b>  (30) Priority Data: <table border="0"> <tr><td>60/064,911</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,912</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,983</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,900</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,988</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,987</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,908</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,984</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>60/064,985</td><td>7 November 1997 (07.11.97)</td><td>US</td></tr> <tr><td>06/066,094</td><td>17 November 1997 (17.11.97)</td><td>US</td></tr> <tr><td>06/066,100</td><td>17 November 1997 (17.11.97)</td><td>US</td></tr> <tr><td>06/066,089</td><td>17 November 1997 (17.11.97)</td><td>US</td></tr> <tr><td>06/066,095</td><td>17 November 1997 (17.11.97)</td><td>US</td></tr> <tr><td>06/066,090</td><td>17 November 1997 (17.11.97)</td><td>US</td></tr> </table> (71) Applicant (for all designated States except US): <b>HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).</b>		60/064,911	7 November 1997 (07.11.97)	US	60/064,912	7 November 1997 (07.11.97)	US	60/064,983	7 November 1997 (07.11.97)	US	60/064,900	7 November 1997 (07.11.97)	US	60/064,988	7 November 1997 (07.11.97)	US	60/064,987	7 November 1997 (07.11.97)	US	60/064,908	7 November 1997 (07.11.97)	US	60/064,984	7 November 1997 (07.11.97)	US	60/064,985	7 November 1997 (07.11.97)	US	06/066,094	17 November 1997 (17.11.97)	US	06/066,100	17 November 1997 (17.11.97)	US	06/066,089	17 November 1997 (17.11.97)	US	06/066,095	17 November 1997 (17.11.97)	US	06/066,090	17 November 1997 (17.11.97)	US	(72) Inventors; and (75) Inventors/Applicants (for US only): <b>FENG, Ping [CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US). CARTER, Kenneth, C. [US/US]; 11601 Brandy Hall Lane, North Potomac, MD 20878 (US). ENDRESS, Gregory, A. [US/US]; 9729 Clagett Farm Drive, Potomac, MD 20854 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). JANAT, Fouad [US/US]; 140 High Street #202, Westerly, RI 02891 (US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US). WEI, Ying-Fei [CN/US]; 1714-C Marina Court, San Mateo, CA 94403 (US). MOORE, Paul, A. [GB/US]; 19005 Leatherbark Drive, Germantown, MD 20874 (US). SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place, Centreville, VA 22020 (US). KYAW, Hla [MM/US]; 520 Sugarbush Circle, Frederick, MD 21703 (US). LaFLEUR, David, W. [CN/US]; 3142 Quesada Street, N.W., Washington, DC 20015 (US). OLSEN, Henrik, S. [DK/US]; 182 Kendrick Place #24, Gaithersburg, MD 20878 (US). SHI, Yanggu [CN/US]; 437 West Side Drive #102, Gaithersburg, MD 20878 (US). EBNER, Reinhard [DE/US]; 9906 Shelburne Terrace #316, Gaithersburg, MD 20878 (US).</b>  (74) Agents: <b>HOOVER, Kenley, K. et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).</b>  (81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.</i> <i>With an indication in relation to deposited biological material furnished under Rule 13bis separately from the description.</i>	
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(54) Title: <b>125 HUMAN SECRETED PROTEINS</b>																																													
(57) Abstract																																													
<p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>																																													

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## 125 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and  
5 their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or  
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum  
15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

20 Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or  
25 secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include  
30 the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using  
35 secreted proteins or the genes that encode them.

### *Summary of the Invention*

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### *Detailed Description*

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig

analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,  
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained  
10 in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the  
15 filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages  
20 of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even  
25 lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include  
30 Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such  
35 as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

5           The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be  
10           single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and  
15           unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

          The polypeptide of the present invention can be composed of amino acids joined  
20           to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs,  
25           as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be  
30           branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a  
35           nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

## **Polynucleotides and Polypeptides of the Invention**

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

The translation product of this gene shares sequence homology with transcytosis-associated protein (TAP), which is thought to be important in the docking of transport vesicles with their target membrane. The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in developing brain, other embryonic tissue and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain as well as other developmental anomalies or fetal deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. embryonic, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:136 as residues: Pro-51 to Arg-56, Lys-89 to Gln-94, Glu-144 to Gln-151, Gln-178 to Gln-183, Leu-224 to Gln-229, Tyr-284 to Pro-298, Lys-324 to Lys-334.

The tissue distribution in developing brain and placental tissues and the homology to transcytosis-associated protein (TAP) indicates that polynucleotides and polypeptides corresponding to this gene are useful for a host of conditions which arise as a result of a failure of, or deficiency in, the secretory or endocytic pathway. In addition, the expression in brain would suggest a role in the detection and treatment of brain tumors, developmental and behavioral disorders such as mania, depression, paranoia, addictive behavior and sleep disorders. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 996 of SEQ ID NO:11, b is an integer of 15 to

1010, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 2

This gene is expressed primarily in human adrenal gland tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine disorders, particularly adrenal gland tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adrenal gland, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. endocrine, adrenal gland, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of adrenal gland tumors. Furthermore, polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addisoni's disease, Cushingi's Syndrome, and disorders and/or cancers of the pancrease (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 1545 of SEQ ID NO:12, b is an integer of 15 to 1559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

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### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in small intestine.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, a variety of gastrointestinal disorders including duodenal ulcers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. gastrointestinal, smooth muscle, endothelial, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:138 as residues: Gln-77 to Pro-86.

The tissue distribution in small intestine indicates that the translation product of this gene is useful for the diagnosis and/or treatment of a number of disorders having to do with the gastrointestinal system, and specifically the small intestine, such as obstructions of the ileum, meckel's diverticulum, Crohn's disease, celiac sprue, tropical

sprue, and lymphoma. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:13, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 4**

The translation product of this gene shares sequence homology with the mouse astrotactin protein, which is thought to be important in supporting neuronal migration along glial fibers. Additionally, astrotactin is thought to act as a ligand for neuron-glial binding during neuronal migration. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in brain tissue from a patient with Alzheimer's disease.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural or CNS disorders, particularly neurodegenerative disorders such as Alzheimer's disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the

expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:139 as residues: Gln-43 to Trp-53, Arg-69 to Ser-76.

5       The tissue distribution in brain combined with the homology to mouse astrotactin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of CNS diseases, such as Alzheimer's disease. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural  
10 disorders, or inflammatory conditions such as Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS,  
15 psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the  
20 gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25       Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

30       Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1241 of SEQ ID NO:14, b is an integer of 15 to 1255, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

35

## FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with transporter protein, which is thought to be important in metabolic and respiratory functions.

5        This gene is expressed primarily in T-cell lymphoma and dendritic cells, and to a lesser extent in placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic disorders, particularly cancer including T-cell lymphoma and disorders associated with embryogenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:140 as residues: Thr-87 to Trp-94.

The tissue distribution in T-cell lymphoma and dendritic cells and the homology to transporter protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of haemopoietic disorders such as cancer, particularly T-cell lymphoma and disorders associated with embryogenesis. Furthermore, this gene product may play a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in T cells and primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 1177 of SEQ ID NO:15, b is an integer of 15 to 1191, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 6

This gene is expressed primarily in the liver, and to a lesser extent, in testis.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic, reproductive, or endocrine disorders, particularly hepatoma or male infertility. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s)  
15 or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. hepatic, reproductive, endocrine, testical, immune, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, seminal fluid, plasma, urine, synovial fluid and  
20 spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:141 as residues: Ser-21 to Trp-34, Cys-68 to Gly-89, Cys-122 to Phe-133.

25 The tissue distribution in liver tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of liver disorders, particularly those affecting the immune and hematopoietic systems such as hepatomas. Furthermore, the protein product of this gene would also be useful for the detection and treatment hepatoblastoma, jaundice, hepatitis, or liver metabolic  
30 diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. Furthermore, the expression within testis indicates that the protein may show utility in the treatment and/or detection of a variety of reproductive disorders such as male infertility, impotence, and may even be useful as a contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
35 and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more  
 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1172 of SEQ ID NO:16, b is an integer of 15 to 1186, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

The translation product of this gene shares sequence homology with urokinase receptor which is thought to be important in cell matrix remodeling and cell movement.

- 15 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

FYIADHSFTARPTLRMFRISAVVATDKMTFTSGGTTFGDGCASSVA GEVMNC  
 QTVLCILWTPFVFCPSIAVIIIICVFTSKALEAIWKWCRVERRPHIIEVDVLGKCP  
 AF (SEQ ID NO:261), RPTLRMFRISAVVATDKMTFTSGGT (SEQ ID NO:262),

- 20 PSIAVIIIICVFTSKALEAIWKWCRVER (SEQ ID NO:263), TSVSFHHRYKSS  
 DRPAHKVS (SEQ ID NO:264). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal lung, breast, and Hodgkin's  
 Lymphoma II.

- 25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary, reproductive, immune, or hematopoietic disorders, particularly cell growth and differentiation conditions. Similarly, polypeptides and  
 30 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal lung, breast, and tissues involved in Hodgkin's Lymphoma II expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Pulmonary,  
 35 immune, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, amniotic fluid, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual

having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:142 as residues: Asn-32 to Asp-38, Thr-40 to Phe-46, Asn-53 to Gln-74, Ser-84 to Ile-91, Cys-95 to Glu-100, Ser-109 to Cys-121.

The tissue distribution in proliferating and differentiating tissues, combined with the homology to a urokinase receptor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cell growth and differentiation disorders, particularly of the lung, renal, breast, immune and endothelial tissues. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1168 of SEQ ID NO:17, b is an integer of 15 to 1182, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

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## **FEATURES OF PROTEIN ENCODED BY GENE NO: 8**

The translation product of this gene shares sequence homology with cell adhesion molecules, which are implicated in cell migration, axonal guidance and fasciculation, and growth and tumorigenesis. When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid

cells, including their progenitors, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

RHNDFNKLSYTECNNMNKRMAKPEKKKGSVKSSLGIFLGPNCHLISSLFLFS  
 10 VSLYPFATQF PFHYVLIFIIQAFGLCLPLTERQEAKSGLGGLCPDYTWPC  
 PCLLVSCLSLRL (SEQ ID NO:265), CEVFSWHFPWSKLSPHLFLVSFLCIPL  
 SLCHTV SFLCSNIYNPGLRTMLAPHRETGGQVWAGWALSRLHVALPMSLG  
 VLSLPAPTVTVVRMEGGDWKVCEQL GQCTYSHRMTK (SEQ ID NO:266),  
 KRMAKPEKKKGSVKSSLGIFLGP (SEQ ID NO:267), and/or YNPGLRTMLA  
 15 PHRETGGQVWAGWALSRLHVA (SEQ ID NO:268). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the meningioma, melanocytes, and to a lesser extent, in breast.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disease states and behavioral disorders, in addition to integumentary or reproductive disorders, particularly of the breast. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
 25 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. neural, integumentary, breast, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine,  
 30 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 35 NO:143 as residues: Asn-71 to Asp-79.

The tissue distribution in meningioma combined with the homology to cell adhesion molecules and the detected GAS biological activity indicates that

polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

- 5 Moreover, the expression within melanocytes and breast tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, 10 erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various 20 connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, This protein may show utility in 25 modulating the immune systems response to various degenerative neural conditions based upon the detected GAS biological activity. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1157 of SEQ ID NO:18, b is an integer of 15

to 1171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 9

This gene is expressed primarily in fetal liver and spleen, and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, neural, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:144 as residues: Thr-187 to Lys-192, Asn-255 to Leu-262.

The tissue distribution of this gene in fetal liver spleen indicates a key role in the development of the immune system. Thus this gene could be used in the treatment and/or detection of immune disorders including arthritis, asthma, immunodeficiency diseases and leukemia. Expression in infant brain also indicates a role in the treatment and/or detection of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntintons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Moreover, expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1323 of SEQ ID NO:19, b is an integer of 15 to 1337, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

## **15 FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

This gene is expressed primarily in breast, and to a lesser extent in liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer, hepatoblastoma, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast and liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. breast, liver, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:145 as residues: Gln-29 to Gly-38, Lys-57 to Asp-62.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases), and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In

addition, the expression in breast would suggest a possible role in the detection and treatment of breast cancer.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1148 of SEQ ID NO:20, b is an integer of 15 to 1162, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 11

This gene is expressed primarily in brain, and to a lesser extent in retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, degenerative and behavioral diseases of the brain such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders as well as conditions that affect vision and function of the eye such as retinoblastoma and cataracts. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and eye, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, retina, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:146 as residues: Pro-46 to Gln-60, Pro-68 to Gly-75, Leu-78 to Ala-86, Gln-93 to Asp-98.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental, degenerative and behavioral diseases, and conditions of the brain such as aphasia, depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. In addition, the expression in retina would also suggest a role for this gene product in the diagnosis and treatment of conditions that affect vision and function of the eye such as retinoblastoma, myopia, hyperopia and cataracts.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1823 of SEQ ID NO:21, b is an integer of 15 to 1837, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

20

## FEATURES OF PROTEIN ENCODED BY GENE NO: 12

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8. One embodiment of this gene comprises polypeptides of the following amino acid sequence:

MSPYASQGFPLPPYPPQEANRSITSLSVADTVSSSTTSHTTAKPAAPSFGLVLSN  
LPLPIPTVDASIPTSQNGFGYKMPDVPDAFPELSELSVSQLTDMNEQEEVLLEQF  
LTLPLKQIITDKDDL VKSIEELARKNLLLEPSLEAKRQTVLDKYELLTQMKSTF  
EKKMQRQHELSESCSASALQARLKVAAHEAEEESDNI AEDFLEGKMEIDDFLSS  
FMEKRTICHCRRAKEEKLQQAIA MHSQFHAPL (SEQ ID NO:269), LPPYPPQE  
ANRSITSLSVADTVS (SEQ ID NO:270), TAKPAAPSFGLVLSNLPLPIPTVDASIP  
(SEQ ID NO:271), PDVPDAFPELSELSVSQLTDMNEQE (SEQ ID NO:272), QFLT  
LPLKQIITDKDDL VKSIEELARKN (SEQ ID NO:273), RQTVLDKYELLTQ MKS  
TFEKKMQRQ (SEQ ID NO:274), ASALQARLKVAAHEAEEESDNI AEDFLE (SEQ  
ID NO:275), and/or MEKRTICHCRRAKEEKLQQAIA MHSQF )SEQ ID NO: 276).  
An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in breast and placenta, and to a lesser extent in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast and endometrial cancers as well as prenatal disorders and deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. breast, placental, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of breast cancer, ovarian and other endometrial cancers, infertility and pre-natal disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1040 of SEQ ID NO:22, b is an integer of 15

to 1054, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 13

This gene is expressed primarily in anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly autoimmune disorders such as lupus. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:148 as residues: Lys-49 to Gln-57, Arg-63 to Ala-69.

The tissue distribution in T-cells indicates that the polypeptides or polynucleotides are useful for treatment, prophylaxis, and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. The expression observed predominately in hematopoietic cells also indicates that the polynucleotides or polypeptides are important in treating and/or detecting hematopoietic disorders, such as graft versus host reaction, graft versus host disease, transplant rejection, myelogenous leukemia, bone marrow fibrosis, and myeloproliferative disease. The polypeptides or polynucleotides are also useful to enhance or protect proliferation, differentiation, and functional activation of hematopoietic progenitor cells (e.g., bone marrow cells), useful in treating cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. The polypeptides or polynucleotides are also useful to increase the proliferation of peripheral blood leukocytes, which can be used in the combat of a range of hematopoietic disorders, including immunodeficiency diseases, leukemia,

and septicemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:23, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

#### 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 14

The translation product of this gene shares sequence homology with a drought-induced protease inhibitor from soybean. As a result, the protein product of this gene may show utility in the treatment and/or prevention of a variety of proliferative disorders (e.g. for inhibition of key proteolytic events during cellular metabolism of the tumor which may lead to cessation of mitosis) or for the treatment of degenerative conditions where the inhibition of aberrant proteolysis may lead to cessation of degeneration and ultimately in immune protection.

This gene is expressed primarily in the kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. kidney, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:149 as residues: Glu-48 to Arg-56, Ser-61 to Gly-66.

The tissue distribution in kidney tissue combined with the homology to a protease inhibitor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the kidney. Furthermore, this gene or gene product could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 914 of SEQ ID NO:24, b is an integer of 15 to 928, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

25

## **FEATURES OF PROTEIN ENCODED BY GENE NO: 15**

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

TRPVFLSMTPLKGIKSVILPQVFLCAYMAAFNSINGNRSYTCKPLERSLLMAGA  
VASSTFLGVIPQFVQ (SEQ ID NO:277), PLKGIKSVILPQVFLCAYMAA (SEQ ID  
NO:278), and/or AFNSINGNRSYTCKPLERSLL (SEQ ID NO:279). Polynucleotides  
encoding these polypeptides are also encompassed by the invention. The gene encoding  
5 the disclosed cDNA is believed to reside on chromosome 10. Accordingly,  
polynucleotides related to this invention are useful as a marker in linkage analysis for  
chromosome 10.

This gene is expressed primarily in B cell and T cell lymphomas.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, immune or hematopoietic disorders, particularly B cell and T cell  
lymphomas, infections, multiple myeloma, immunodeficiencies, and inflammatory  
conditions. Similarly, polypeptides and antibodies directed to these polypeptides are  
15 useful in providing immunological probes for differential identification of the tissue(s)  
or cell type(s). For a number of disorders of the above tissues or cells, particularly  
immune or hematopoietic disorders, such as B- and T-cell lymphomas, expression of  
this gene at significantly higher or lower levels may be routinely detected in certain  
tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded  
20 tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal  
fluid) or another tissue or cell sample taken from an individual having such a disorder,  
relative to the standard gene expression level, i.e., the expression level in healthy tissue  
or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
25 NO:150 as residues: Phe-85 to Gly-96, Glu-133 to Thr-143.

The tissue distribution in B- and T-cell lymphomas, combined with the detected  
GAS biological activity indicates that polynucleotides and polypeptides corresponding  
to this gene are useful for the diagnosis and treatment of a variety of immune disorders,  
particularly proliferative conditions such as cancer and leukemias. In addition,  
30 polynucleotides and polypeptides corresponding to this gene are useful for the treatment  
and diagnosis of hematopoietic related disorders such as anemia, pancytopenia,  
leukopenia, thrombocytopenia or leukemia since stromal cells are important in the  
production of cells of hematopoietic lineages. The uses include bone marrow cell ex  
vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or  
35 chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis,  
therefore, it can be used in immune disorders such as infection, inflammation, allergy,  
immunodeficiency etc. In addition, this gene product may have commercial utility in the

expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 952 of SEQ ID NO:25, b is an integer of 15 to 966, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 16

- 20 The protein product of this gene was found to have homology to the Poly(A) polymerase of *Bos taurus*, which is known to be important in the creation of the 3' poly(A) tail of mRNA's. The gene encoding the disclosed cDNA is believed to reside on chromosome 14. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 14.

This gene is expressed primarily in brain, and to a lesser extent, in prostate.

- 25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, such as neurodegenerative disease states and behavioral conditions, in addition to reproductive disorders, particularly of the prostate. Similarly,
- 30 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. neural, reproductive, and cancerous and wounded
- 35 tissues) or bodily fluids (e.g. lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:151 as residues: Glu-47 to Ser-52.

5           The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Moreover, expression of the gene in prostate  
10 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection or treatment of prostate disorders including benign prostate hyperplasia, prostate cancer, and metabolic disorders. The homology to the PAP polyA polymerase indicates that the protein product of this gene, antibodies directed to this protein, or the gene encoding this protein via a gene therapy approach, may show utility as a  
15 preventative therapy for proliferative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
20 ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
25 a-b, where a is any integer between 1 to 1132 of SEQ ID NO:26, b is an integer of 15 to 1146, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

### 30   **FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

This gene is expressed primarily in epididymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the reproductive organs. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes

for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:152 as residues: Met-1 to Pro-6, Glu-58 to Cys-63, Glu-65 to Gly-72, Thr-74 to Val-87.

The tissue distribution in epididymus indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders of the epididymus and reproductive organs. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 788 of SEQ ID NO:27, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 18**

5           This gene is expressed primarily in synovium and rhabdomyosarcoma.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscular skeletal system and cancer. Similarly, polypeptides and  
10   antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. musculo-skeletal, cancerous and wounded tissues) or bodily  
15   fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID  
20   NO:153 as residues: Trp-30 to Val-35, Lys-44 to Arg-49.

          The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the muscular skeletal system and cancer. Furthermore, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and  
25   conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as  
30   chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly available  
35   and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1155 of SEQ ID NO:28, b is an integer of 15 to 1169, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 19

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in fetal liver/spleen, and to a lesser extent, in tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, or hepatic disorders, particularly multiple myeloma, immunodeficiencies, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:154 as residues: Asp-27 to Ser-36.

Expression of this gene at either the RNA or protein level could be used as a diagnostic indicator of hepatic cancer. Furthermore, the tissue distribution in fetal liver and tonsil tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Moreover, the protein product of this gene may play a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all

hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1452 of SEQ ID NO:29, b is an integer of 15 to 1466, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

25

## **FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

This gene is expressed primarily in human brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders or diseases of the central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g.

lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5           The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and the treatment of CNS disorders. Furthermore, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons
- 10 Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo,
- 15 sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ
- 20 ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of
- 25 a-b, where a is any integer between 1 to 1212 of SEQ ID NO:30, b is an integer of 15 to 1226, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

### 30   **FEATURES OF PROTEIN ENCODED BY GENE NO: 21**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

- MSDFEKVDISVHQHHVGPLLLMTTESWGPSCAPSPALLSGHTAASFHTLGG
- 35   VLGCPPYHKFYSS AHTSDHRKETNKVEEGRWVDVTRSLGNFNFRRKFFC  
VSELLICGIFLDSSWKLQINSNDCKVL (SEQ ID NO:280), VGPLLMTTESW  
GPSCAPSPALLSGHTAAS (SEQ ID NO:281), and/or ETNKVEEGRWVDVTRS

LGNFNFRRKFF (SEQ ID NO:282). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal spleen or liver, adult spleen, and to a lesser extent, in activated T-cells.

5           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly abnormal proliferation or activation of hematopoietic cells, particularly of T-cells and their progenitors.

10          Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and  
15          cancerous and wounded tissues) or bodily fluids (e.g.lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20           Preferred epitopes include those comprising a sequence shown in SEQ ID NO:156 as residues: Arg-19 to Phe-24, Ala-44 to Asp-51, Glu-60 to Ile-66.

          The tissue distribution in spleen tissues and T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for modulating or detecting the abnormal proliferation or activation of T-cells and immune cell  
25          precursor cells. Moreover, expression within fetal spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture,  
30          bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the  
35          differentiation and/or proliferation of various cell types. Similarly, This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by

boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:31, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in the amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, degenerative and behavioral diseases of the brain such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:157 as residues: Pro-94 to Ala-107.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental, degenerative and behavioral diseases and conditions of the brain such as aphasia, depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, mania, depression, dementia, paranoia, addictive behavior and sleep disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:32, b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 23

30

The translation product of this gene shares sequence homology with octaprenyltransferase, which is thought to be important in cellular respiration and metabolism. When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The

gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

5 This gene is expressed primarily in synovium, liver cells, dendritic cells and stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic and respiratory disorders, immune disorders. Similarly, 10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic processes and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, liver, 15 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:158 as residues: Asp-54 to Asn-69, His-176 to Asp-181, Phe-194 to Trp-201, Ser-220 to Pro-225, Arg-248 to Trp-253, Trp-276 to Ile-288.

The tissue distribution and homology to octaprenyltransferase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment 25 and diagnosis of metabolic and respiratory disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ 30 ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of 35 a-b, where a is any integer between 1 to 1362 of SEQ ID NO:33, b is an integer of 15 to 1376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 24**

5           This gene is expressed primarily in activated T cells and in the spleen from a patient suffering from lymphocytic leukemia.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly immunodeficiencies, multiple myeloma, and leukemias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in T-cells and spleen tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of leukemia. Furthermore, the tissue distribution indicates that the polypeptides or polynucleotides are useful for treatment, prophylaxis, and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. The expression observed predominantly in hematopoietic cells also indicates that the polynucleotides or polypeptides are important in treating and/or detecting hematopoietic disorders, such as graft versus host reaction, graft versus host disease, transplant rejection, myelogenous leukemia, bone marrow fibrosis, and myeloproliferative disease. The polypeptides or polynucleotides are also useful to enhance or protect proliferation, differentiation, and functional activation of hematopoietic progenitor cells (e.g., bone marrow cells), useful in treating cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. The polypeptides or polynucleotides are also useful to increase the proliferation of peripheral blood leukocytes, which can be used in the combat of a range of hematopoietic disorders, including immunodeficiency diseases, leukemia,

and septicemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1206 of SEQ ID NO:34, b is an integer of 15 to 1220, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 25

This gene is expressed primarily in bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly disorders afflicting stem cell or myeloid progenitors, and in particular multiple myeloma, immunodeficiencies, or SCID. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune and hematopoietic systems. In addition, The protein product of this gene is useful for the diagnosis and/or treatment of hematopoietic disorders. Furthermore, this gene product is primarily expressed in hematopoietic cells

and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in bone marrow, which is a primary sites of definitive hematopoiesis. The uses include bone marrow cell ex vivo culture, bone marrow  
5 transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation  
10 and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
15 ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
20 a-b, where a is any integer between 1 to 1332 of SEQ ID NO:35, b is an integer of 15 to 1346, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

## 25    **FEATURES OF PROTEIN ENCODED BY GENE NO: 26**

This gene is expressed primarily in the cells of the immune system.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune systems, such as AIDS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of  
35 this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
5 NO:161 as residues: His-17 to Ser-24, Glu-53 to Asn-58, Glu-66 to Lys-72.

The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Further, the expression of this gene product indicates a role in the regulation of the proliferation; survival; differentiation; and/or  
10 activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein  
15 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells  
20 and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
25 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
30 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:36, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

35

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 27

The translation product of this gene shares sequence homology with glucan synthetase which is thought to be important in modifying carbohydrate moieties on extracellular molecules.

5 This gene is expressed primarily in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly autoimmune diseases and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:162 as residues: Gly-33 to Leu-39, Thr-69 to Ser-77, Arg-102 to Thr-109.

The tissue distribution in T-cells combined with the homology to glucan synthetase indicates that polynucleotides and polypeptides corresponding to this gene are useful for modifying the response and production of active cytokines by T cells, modulating cell-cell interactions, or cell-tissue interactions, and in inflammatory conditions. Alternatively, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease,

scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:37, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 28

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

GRGDKPRQDRPASLRLKGPPSCQAPASHSSTLSSHCPCSLFACGSVWPGSLGS  
GIFARLSQLLPSPASWG WDFLTRQAQQMLGPSLCPGHSTSAHQHYGAYVLP  
RDLCSFLLTSTVQGTAPLKNSRVTCIGSQQVPLC (SEQ ID NO:283), AEVTSPA  
KTDLQVFVSRDLPHARPLPLTAAPFPLIVPVPFLPVDLFGQGPWGQEYLQDSAS  
SFPAQPLGA GTFSPCGRHNRCDPVSAQVTAQVHISTMGPMSCPETSAPSC  
SHPQFRARRPSRTPEPVSSAPSKCLFV YDVPLL (SEQ ID NO:284), SLRLKGP  
PSCQAPASHSSTLSSHCPCSLFA (SEQ ID NO:285), QQMLGPSLCPGHS TSAH  
QHYGAYVLPRDLC (SEQ ID NO:286), DLQVFVSRDLPHARPLPLTAAPF PLIV  
PVPF (SEQ ID NO:287), AQVHISTMGPMSCPETSAPSCSHPQFRARRP SRTPE  
SPV (SEQ ID NO:288), and/or QAPPRQTCKSSSQGTSL (SEQ ID NO:289).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in endometrial tumors, fetal spleen, and to a lesser extent, in activated monocytes and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, reproductive, immune, hematopoietic disorders, particularly pregnancy defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. reproductive, endometrial, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:163 as residues: Ser-66 to Thr-75.

The tissue distribution in endometrial tissue indicates that the protein product of this gene could be used in the treatment and/or detection of pregnancy associated disorders including miscarriage, and endometriosis. Alternatively, expression in hematopoietic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of immune system related diseases including arthritis, asthma, immunodeficiency diseases and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 692 of SEQ ID NO:38, b is an integer of 15 to 706, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 29

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

AALRPSGSLAGPEWPWQHWCGCWREHXVKPQQVDLHSARLWAAPAAVGPA  
 HAGGSPGMPPGGTAPHARRH SLPSPTAQSHLWHVHGLRQRGPKAVPLDLAQ  
 LVTTTTPLFXLALSALLLGRRHPLQLAAMGPLCLGAAC SLAGEFRTPTT  
 GCGFLLAATCLRGLKSVQQSALLQEERLDAVTLLYATSLPSFCLLAGAALVLEA  
 5 GVAPP PTAGDSRLWACILLSCLLSVLYNLASFSLALTSALT VHV LGNLTVV  
 GNLILSRL LFGSRLSALS YVGIA LTL SGMFLYHNCEFVASWAARRGLW  
 RRDQPSKGL (SEQ ID NO:290), GQPSGPPAAWPGPSGHGSTGVAAGGSTXSSL  
 NKWIFTVHGFGRPLLLSALHMLVAALACHRGARRP (SEQ ID NO:291), WGPS  
 GHGSTGVAAGGSTXSS (SEQ ID NO:292), EWPWQHWCGCWREHXVKPQQVD  
 10 LHSA (SEQ ID NO:293), QQSALLQEERLDAVTLLYATSLPSFCLL (SEQ ID  
 NO:294), ACILLSCLLSVLYNLASFSLALTSAL (SEQ ID NO:295), and/or  
 SLNKWIFTVHGFGRPLLLSAL (SEQ ID NO:296). Polynucleotides encoding these  
 polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain tissue from a patient suffering from  
 15 Alzheimer's disease (spongy change), and to a lesser extent, in human umbilical vein  
 and human pancreas tumor tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 20 not limited to, developmental, immune, metabolic, digestive or neural disorders, such  
 as Alzheimer's disease, in addition to cancers and tumors. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the immune and secretory systems,  
 25 expression of this gene at significantly higher or lower levels may be routinely detected  
 in certain tissues and cell types (e.g. developmental, immune, metabolic, digestive,  
 cancerous and wounded tissues) or bodily fluids (e.g. lymph, bile, amniotic fluid,  
 serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
 taken from an individual having such a disorder, relative to the standard gene  
 30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

The tissue distribution in brain tissue indicates that polynucleotides and  
 polypeptides corresponding to this gene are useful for diagnosis and treatment of  
 Alzheimer's disease, and immune and secretory system disorders such as cancers.  
 35 Moreover, polynucleotides and polypeptides corresponding to this gene are useful for  
 the detection/treatment of neurodegenerative disease states, behavioural disorders, or  
 inflammatory conditions such as Parkinsons Disease, Huntingtons Disease, Tourette

Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1333 of SEQ ID NO:39, b is an integer of 15 to 1347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 30**

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infection and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:165 as residues: Asn-43 to Ala-49.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of infection and inflammation related immune diseases. Furthermore, the gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1453 of SEQ ID NO:40, b is an integer of 15 to 1467, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 31

30

The translation product of this gene shares sequence homology with Ly6C antigen, which is thought to be important in T-cell activation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

KSTLSAAVVATILRTLA (SEQ ID NO:297), GDHSEQCLIKEMGARERRFCKAR  
 35 GYRDTG REAQAKAGGRRGSQWNEQCS SQRPRPAKEVRKTRPRAGVGRGP  
 ALLQLSLLQQVVLVVRPSLRLVWLKA S (SEQ ID NO:298), MERGEYGGWG  
 TYGSLDLGSQQLCTVRSSGPCSLHWGQH RSPISGPDNPSSSR GQQSIGSK

VGSPRSQWRSWKEVGRDPEKGE (SEQ ID NO:299), QAKAGGRRGSQWNESQ  
CSSQRPR (SEQ ID NO:300), VGRGPALLQL SLLQQVVL YVRPSLRL (SEQ ID  
NO:301), YGSLDLGSQLCTVRSSGPCGSL (SEQ ID NO:302), and/or KVGSPSR  
SQWRSWKEVGRDP (SEQ ID NO:303). Polynucleotides encoding these polypeptides  
5 are also encompassed by the invention.

This gene is expressed primarily in bone cancer, fetal brain, lung, and adipose  
tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
10 biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, skeletal, developmental, pulmonary, or metabolic disorders, particular  
disorders in the immune responses to the above conditions, such as in autoimmunities.  
Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
15 type(s). For a number of disorders of the above tissues or cells, particularly of the  
immune system, expression of this gene at significantly higher or lower levels may be  
routinely detected in certain tissues or cell types (e.g. skeletal, developmental,  
pulmonary, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g.  
lymph, amniotic fluid, pulmonary surfactant or sputum, serum, plasma, urine, synovial  
20 fluid and spinal fluid) or another tissue or cell sample taken from an individual having  
such a disorder, relative to the standard gene expression level, i.e., the expression level  
in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
NO:166 as residues: Gln-37 to Gln-45, Phe-76 to Leu-83, Thr-89 to Thr-105.

25 The tissue distribution combined with the homology to the Ly6C T-cell  
activation antigen indicates that polynucleotides and polypeptides corresponding to this  
gene are useful for the diagnosis and intervention of immune related disorders. The  
tissue distribution in tissues particularly active in immune reaction, for example bone  
cancer, indicate that this gene may also be involved in T-cell activation. Thus the gene  
30 product can be used either for the development of immune suppressants, or modulators,  
for immune responses. Moreover, the expression within brain tissue indicates that the  
protein is useful for the treatment and/or prevention of neurodegenerative disorders,  
particularly, but not limited to, Alzheimer's or Parkinson's disease. Alternatively, the  
expression within fetal tissue and other cellular sources marked by proliferating cells  
35 indicates that this protein may play a role in the regulation of cellular division, and may  
show utility in the diagnosis and treatment of cancer and other proliferative disorders.  
Similarly, developmental tissues rely on decisions involving cell differentiation and/or

apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 900 of SEQ ID NO:41, b is an integer of 15 to 914, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 32

- The gene encoding the disclosed cDNA is thought to reside on chromosome 12.
- 20 Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in brain, keratinocytes and fibroblasts.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the brain and epidermal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermal and neural systems,
- 25 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. skin, brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily
- 30 fluid from an individual not having the disorder.

35

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of diseases of the

neural and epidermal systems. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and perception. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Pageti's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm).

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1117 of SEQ ID NO:42, b is an integer of 15 to 1131, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

### 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The translation product of this gene shares sequence homology with a sodium dependent sulfate transporter which is thought to be important in sulfate uptake by cells. The gene encoding the disclosed cDNA is thought to reside on chromosome 7.

Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7. One embodiment of this gene comprises polypeptides of the following amino acid sequence:

MPQSLSSSLASSSSSFQRXKPCFGKKNDGENQEHS LGTEPIITWKDFQKTMPWE  
 IVILVGGGYALASGSKSSGLSTWIGNQMLS LSSLPPWAVTLLACILVSIVTEFVS  
 NPATITIFLPILCSLSETLHINPLYTLIPVTMCISFAVMLPVG NPPNAIVFSYGHCC  
 10 IKDMVKAGLG VNVIGLVIVMVAINTWGVSLFHLDTYPAWARVSNITDQA (SEQ  
 ID NO:304), NDGENQEHS LGTEPIITWKDFQK (SEQ ID NO:305), IGNQMLS LSS  
 LPPWAVTLLACILV (SEQ ID NO:306), ATITIFLPILCSLSETLHINPLYTLIP (SEQ  
 ID NO:307), LPVG NPPNAIVFSYGHCCIKDMVKAG (SEQ ID NO:308), and/or  
 LVIVMVAINTWGVSLFHLDTYPAWARVSN (SEQ ID NO:309). An additional  
 15 embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in placenta, and to a lesser extent, in infant brain and spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic, reproductive, or central nervous system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous  
 25 system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. CNS, reproductive, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression  
 30 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placental and neural tissues, combined with the homology to a sodium dependent sulfate transporter indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of metabolic  
 35 disorders involving sodium and sulfate metabolism and CNS disorders involving neuronal signalling abnormalities. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative

disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:43, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 34**

Contact of cells with supernatant expressing the product of this gene increases the permeability of bovine chondrocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the chondrocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating chondrocyte cells.

This gene is expressed primarily in CD34 positive cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or reproductive disorders, particularly diseases related to lymphocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. bone, immune, hematopoietic, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:169 as residues: Leu-26 to Arg-32, Asn-40 to Ser-46.

The tissue distribution in CD34 positive cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of the diseases of the immune system particularly those related to T lymphocytes. Furthermore, the tissue distribution, as well as the detected calcium flux biological activity data, suggest that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of bone and hematopoietic disorders. The ability of the translation product of this gene to induce a calcium flux in chondrocytes indicates that it may play a role in the survival, proliferation, and/or growth of bone. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. More generally, as evidenced by expression in CD34 positive cells, this gene may play a role in the survival, proliferation, and/or differentiation of hematopoietic cells, and may be of use in the augmentation of the numbers of stem cells and committed progenitors. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 990 of SEQ ID NO:44, b is an integer of 15 to 1004, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 35

The gene encoding the disclosed cDNA is thought to reside on chromosome 9. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 9.

This gene is expressed primarily in the brain, and to a lesser extent, in liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the brain, central nervous system, or liver, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, hematopoietic, or central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, liver, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and liver tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune, hematopoietic, or central nervous systems. Furthermore, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Alternatively, the

expression within hepatic tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells).

- 5 Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1480 of SEQ ID NO:45, b is an integer of 15 to 1494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 36

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When tested against U937 and Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid and T-cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

ETCPSNGIELRQAPTSLYILLHHIQPTPTHMLGRSYVLPAFSXNXEHGGLPNQI  
 PKGDRNGNIRHSRIT FPCSSSTLQPESH LGFIRSKLHGLVRPGKDLRGRRSL  
 QLSKHSLSSTCYMLRWETYKQVSYTAV (SEQ ID NO:310), QRHQENDKRNH  
 RFLHTCVHMPMCTHTHTQAVLSTWEGQFSNVASFTSLKRIPLSII YIHSSHSP  
 35 RRFVKVCQLRQEKALEL TEVYVSASLKLQLYHLHCHFHTAV (SEQ ID NO:311),  
 RQAPTSLYILLHHIQPTPTHMLG (SEQ ID NO:312), SHLGFIRSKLHGLVRPG  
 KDLRGRRS (SEQ ID NO:313), RNVHRFLHTCVHMPMCTHTHTQ (SEQ ID

NO:314), and/or QLRQEKALELTEVYVSASLKLQLYH (SEQ ID NO:315).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, diseases of the immune system, particularly neutropenia, cancer,  
inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to  
these polypeptides are useful in providing immunological probes for differential  
10 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the immune system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues and cell  
types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily  
fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another  
15 tissue or cell sample taken from an individual having such a disorder, relative to the  
standard gene expression level, i.e., the expression level in healthy tissue or bodily  
fluid from an individual not having the disorder.

The tissue distribution in neutrophils, combined with the detected GAS  
biological activity indicates that polynucleotides and polypeptides corresponding to this  
20 gene are useful for treatment/diagnosis of diseases of the immune system since  
expression is primarily in neutrophils, and may be useful as a growth factor for the  
differentiation or proliferation of neutrophils for the treatment of neutropenia following  
chemotherapy or may be useful in the treatment of immune dysfunction or anti-  
inflammatory by inhibiting infiltration of neutrophils to the site of injury or distress.  
25 Protein, as well as, antibodies directed against the protein may show utility as a tumor  
marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
and accessible through sequence databases. Some of these sequences are related to SEQ  
ID NO:46 and may have been publicly available prior to conception of the present  
30 invention. Preferably, such related polynucleotides are specifically excluded from the  
scope of the present invention. To list every related sequence is cumbersome.  
Accordingly, preferably excluded from the present invention are one or more  
polynucleotides comprising a nucleotide sequence described by the general formula of  
a-b, where a is any integer between 1 to 1152 of SEQ ID NO:46, b is an integer of 15  
35 to 1166, where both a and b correspond to the positions of nucleotide residues shown  
in SEQ ID NO:46, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 37

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PRVRGRKEPGCLGPGRAGGDSQKEIGSWQQM (SEQ ID NO:316), LSKGNRIMAADDDNGDGTSLFDVFSASPLKNNDEGSLDIYA GLDSAVSDSA SKSCVPSRNCLDLYEELTEEGTAKEATYNDLQVEYGKCQ LQMKELMKKFKEIQTQNFSLINENQSLKKN ISALIKTARVEINRKDEEI  
 10 SNLHQKIVLSFHIFEIIIKLQGHILQLKQKILNLDLHIWMIVQRLITRAKS DVSKD VHHSTSLPNLEKEGKPHSDKRSTSHLPTSVEKHCTNGVWSRSHYQVGEGSSN EDSRRGRKDIRHS QFNRGTERVRKDLSTGCGDGEPRILEASQRLQGTS (SEQ ID NO:317), NRIMAADDDNGDGTSLFDVFSASPLKN (SEQ ID NO:318), CLDLY EEILTEEGTAKEATYNDL (SEQ ID NO:319), DEEISNLHQKIVLSFHIFEIIIKLQG  
 15 (SEQ ID NO:320), EKEGKPHSDKRSTSHLPTSVEK (SEQ ID NO:321), and/or TERVRKDLSTGCGDGEPRILEASQRL (SEQ ID NO:322). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 25 of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression  
 30 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune and inflammatory disorders. Furthermore, expression of this gene product in tonsils  
 35 indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma,

5 immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue

10 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show

15 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

20 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1522 of SEQ ID NO:47, b is an integer of 15 to 1536, where both a and b correspond to the positions of nucleotide residues shown

25 in SEQ ID NO:47, and where b is greater than or equal to a + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

30 Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of chondrocytes to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both chondrocytes, in addition to other cell lines or tissue cell types.

35 Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating chondrocytes. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH

and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

- 5 KSYFRTMGGTKRGIKKLVNVCLKHPKNTSLSQQLVFAKINKILISKTTK  
STNLKGLKCLPLSVSIHPTFIYYKHNTTLRIVFGTYFDFFPYRKNKDQAFEGE  
DWESSLNVSDAW (SEQ ID NO:323), TKRGIKKLVNVCLKHPKNTSLS (SEQ ID  
NO:324), and/or SIHPTFIYYKHNTTLRIVFGTYFDFF (SEQ ID NO:325).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

- 10 The gene encoding the disclosed cDNA is believed to reside on chromosome 3.  
Accordingly, polynucleotides related to this invention are useful as a marker in linkage  
analysis for chromosome 3.

This gene is expressed primarily in resting T-cells, and to a lesser extent, in  
retina and placenta.

- 15 Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, immune, reproductive, or eye disorders. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
20 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the immune system, expression of this gene  
at significantly higher or lower levels may be routinely detected in certain tissues and  
cell types (e.g. Immune, hematopoietic, eye, reproductive, and cancerous and  
wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine,  
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual  
having such a disorder, relative to the standard gene expression level, i.e., the  
expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

- Preferred epitopes include those comprising a sequence shown in SEQ ID  
30 NO:173 as residues: Met-1 to Pro-12.

- The tissue distribution of this gene predominantly in T-cells and placenta,  
combined with the detected calcium flux activity indicates that the gene could be  
important for the treatment or detection of immune or hematopoietic disorders including  
arthritis, asthma, immunodeficiency diseases and leukemia. Expression of the gene at  
35 high levels in the retina indicates a role in the treatment and/or detection of eye disorders  
including color blindness, blindness, vision defects, and light sensitivity. Protein, as

well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1024 of SEQ ID NO:48, b is an integer of 15 to 1038, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, degenerative and behavioral diseases of the brain such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:174 as residues: Pro-35 to Met-42.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental,

15

The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the muscular-skeletal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. synovium, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:175 as residues: Pro-15 to Cys-29, Gly-40 to Tyr-54, Pro-72 to His-79.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the muscular skeletal system. Furthermore, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 717 of SEQ ID NO:50, b is an integer of 15 to 731, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 41

The translation product of this gene shares sequence homology with Enoyl-CoA hydratase, which is an RNA binding protein with intrinsic enzymatic activity thought to be important in metabolic disorders. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in fetal liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, liver disorders and cancer. Similarly, polypeptides

and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and metabolic systems, expression of this gene at significantly higher or lower levels may be routinely  
5 detected in certain tissues or cell types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:176 as residues: Pro-10 to Arg-15, Leu-96 to Ser-103, Gly-172 to Pro-178, Gln-213 to Asp-218, Asn-268 to Leu-275, Arg-282 to Phe-289.

The tissue distribution and homology to Enoyl-CoA hydratase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment  
15 and diagnosis of metabolic and liver diseases and cancer. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as,  
20 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present  
25 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1423 of SEQ ID NO:51, b is an integer of 15  
30 to 1437, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 42

35

This gene is expressed primarily in rhabdomyosarcoma tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the muscular skeletal system and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the muscular skeletal system and cancer. Furthermore, the tissue distribution indicates a role in the detection and treatment of disorders and conditions affecting the musculo-skeletal system, in particular rhabdomyosarcomas as well as related cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1355 of SEQ ID NO:52, b is an integer of 15 to 1369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
5 of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
10 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of aberrant immune responses to foreign antigens. Furthermore, expression of this gene  
15 product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is  
20 expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and  
25 psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.  
35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:53, b is an integer of 15

to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 44

This gene is expressed primarily in neutrophils induced with IL-1 and LPS.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly in aberrant neutrophil responses to infection. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:179 as residues: Lys-36 to Cys-42.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a lack of immune response to infection. Furthermore, expression of this gene product in neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion

of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:54, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

This gene is expressed primarily in brain.

- 20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, CNS disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification
- 25 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system (CNS), expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
- 30 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the
- 35 central nervous system. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may

impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1333 of SEQ ID NO:55, b is an integer of 15 to 1347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 46

This gene is expressed primarily in spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly those affecting the spleen, such as in T- and B-cell maturation and their resulting efficacy in the immune response. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, spleen, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:181 as residues: Ser-20 to Ser-34, Thr-40 to Ser-46.

The tissue distribution in spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the spleen and immune system. Furthermore, this gene may play a role in the

survival, proliferation, and/or differentiation of hematopoietic cells in general, and may be of use in the augmentation of the numbers of stem cells and committed progenitors. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:56, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 47

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

QRPHPQPWXPMTLMGTGIPVFAHKMLPFDPPCHLSCTHINPKPXXPQGDEQK  
SQGTEEWCDREGKKRRSI (SEQ ID NO:326), PMTLMGTGIPVFAHKMLPFDP

(SEQ ID NO:327), PPCHLSCTHINPKPXXPQGDE (SEQ ID NO:328), EQKSQGT  
EEWCDREGKKRRSI (SEQ ID NO:329), DEWGAGRMEWEDNLPLEFSCPVT  
KLLSVPSWTPLDAQMLLLFFPSLSHHSSVPWLFCSPPCGXXGLGFI (SEQ ID  
NO:330), EWEDNLPLEFSCPVTKLLSVP (SEQ ID NO:331), PSWTPLDAQM  
5 LLLFFPSLSHH (SEQ ID NO:332), and/or HSSVPWLFCSPPCGXXGLGFI (SEQ  
ID NO:333). Polynucleotides encoding these polypeptides are also encompassed by the  
invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, diseases of the immune system, including neutropenia, cancer,  
inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to  
these polypeptides are useful in providing immunological probes for differential  
15 identification of the tissue(s) or cell type(s). For a number of disorders of the above  
tissues or cells, particularly of the immune system, expression of this gene at  
significantly higher or lower levels may be routinely detected in certain tissues and cell  
types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily  
fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another  
20 tissue or cell sample taken from an individual having such a disorder, relative to the  
standard gene expression level, i.e., the expression level in healthy tissue or bodily  
fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and  
polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases  
25 of the immune system since expression is primarily in neutrophils, and may be useful  
as a growth factor for the differentiation or proliferation of neutrophils for the treatment  
of neutropenia following chemotherapy or may be useful in the treatment of immune  
dysfunction or anti-inflammatory by inhibiting infiltration of neutrophils to the site of  
injury or distress. Protein, as well as, antibodies directed against the protein may show  
30 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
and accessible through sequence databases. Some of these sequences are related to SEQ  
ID NO:57 and may have been publicly available prior to conception of the present  
invention. Preferably, such related polynucleotides are specifically excluded from the  
35 scope of the present invention. To list every related sequence is cumbersome.  
Accordingly, preferably excluded from the present invention are one or more  
polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 522 of SEQ ID NO:57, b is an integer of 15 to 536, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 48

This gene is expressed primarily in prostate, brain and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the reproductive, CNS and immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a  
15 number of disorders of the above tissues or cells, particularly of the reproductive, CNS and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, brain, prostate, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual  
20 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:183 as residues: Asp-26 to Gly-32, Ile-37 to Trp-44.

25 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the reproductive, CNS and immune systems. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such  
30 as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. Additionally, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for  
35 the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression

of this gene product in T cells strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10         Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:58, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 49**

This gene is expressed primarily in frontal cortex of schizophrenics.

- 20           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, CNS diseases and Schizophrenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
- 25          differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
- 30          taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the
- 35          CNS and schizophrenia. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the brain and nervous system. Elevated

expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1255 of SEQ ID NO:59, b is an integer of 15 to 1269, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

This gene is expressed primarily in the testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive or endocrine disorders, particularly for male infertility and testicular cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:185 as residues: His-62 to Ser-74, Leu-99 to Gln-104.

The tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating male infertility. The protein product is likely involved in sperm development and could be administered by injection or related techniques. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the testes and the protein products could be produced. The presence of expression of this gene at either the RNA or protein level could be used as a diagnostic in testicular cancer. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1815 of SEQ ID NO:60, b is an integer of 15 to 1829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 51**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QGLSHIFWMNEQTLK (SEQ ID NO:334). Polynucleotides encoding these polypeptides are also encompassed by the invention.

35

This gene is expressed primarily in activated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, particularly acute inflammatory conditions or autoimmune disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in activated T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for modulating the response of activated T-cells to treat inflammation or autoimmune diseases. The expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more  
 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:61, b is an integer of 15 to 1112, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

10

### FEATURES OF PROTEIN ENCODED BY GENE NO: 52

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element.  
 15 Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the  
 20 binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

- TLVCLGVSSEEGSCPRDVTGPGCCFSLTLTGF (SEQ ID NO:335), ADLIVLWH  
 HHPLWPQHLALPSSGASHDH VELTVYPKTVAASWLELSRPPIFCLFTXPALT  
 25 XHGLDRVAALVECTIWXXXGMWYRRRYSCCQFRDRSI RDVFPEAVMLQQH  
 LRHLAVATYRCRRRSPCKAPTVEEAEGGKPRA VPSGTGFQKHGQEPGGSTSP  
 HFWFG HLQLLVLSVNNRQLFVQGRAGYLEMTGLPCPKLLLTLLRGLT  
 PGVGHGLCAYRRGCLAWRLDXAS (SEQ ID NO:336), ILWRQAPEAPHCSQDSV  
 SSSPRLQEDLAHVTQVTRHPHFRLPSAWCSHSSLLPVSLPRHALATKSPNMX  
 30 XSSPILHLIQFTGQISS PLGGXVQPPGQTASPICTQPM SHPRRQASQQCEQ  
 QLWTGQTSHLQIPCPALNKELPVVDTQDKELQMSPE PMWGCGPSRLLPM  
 LLESCA (SEQ ID NO:337), MLQQHLRHLAVATYRCRRRSPCKAPTVEEAEGGK  
 (SEQ ID NO:338), VTQVTRHPHFRLPSAWCSHSSLLPVSLP (SEQ ID NO:339),  
 and/or GQTASPICTQPM SHPRRQASQQCEQQLW (SEQ ID NO:340).

- 35 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, particularly autoimmune diseases and inflammation.

5 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and  
10 cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:187 as residues: Ser-25 to Lys-33.

The tissue distribution in neutrophils, combined with the detected GAS biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for modulating the response of activated T-cells and other cells of the  
20 immune system involved in inflammation and autoimmune diseases. Similarly, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions.  
25 Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-  
30 graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the  
35 differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:62, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 53

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:  
 FITLRLGPKNMAGVLWRHSNLQTPHYISWCPLLNYRETGNCLLHVSG FLNSR  
 LLANCSGEASGKVIQTLLWPGEISAVA (SEQ ID NO:341), KIRTFLEFSGHRLFST  
 QGQSLTVKAHTAF MLIVKNLRYFLAFKFLMGISDSSEIGLVMQPLQKPHTV  
 ILIRGIEFLSPGGVLP (SEQ ID NO:342), MAGVLWRHSNLQTPHYISWCPLLNYR  
 (SEQ ID NO:343), and/or YFLAFKFLMGISDSSEIGLVMQPLQKPHT (SEQ ID  
 NO:344). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in spleen, and to a lesser extent, in bone marrow and B-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders, particularly multiple myeloma, immunodeficiencies, and infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic disorders, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded

tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5           The tissue distribution of this gene predominantly in hematopoietic cell types and immune tissues indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including arthritis, asthma, immunodeficiency diseases and leukemia. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other  
10       processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis,  
15       granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia,  
20       rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

30       Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1031 of SEQ ID NO:63, b is an integer of 15 to 1045, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

35

## FEATURES OF PROTEIN ENCODED BY GENE NO: 54

The translation product of this gene shares very weak sequence homology with follicle-stimulating hormone beta subunit, which is thought to be important in hormonal regulation. When tested against K562 leukemia cell lines, supernatants removed from cells containing this gene activated the ISRE assay. Thus, it is likely that this gene activates leukemia cells through the Jak-STAT signal transduction pathway. The interferon-sensitive response element is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in adult brain and adipocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and homology to follicle stimulating hormone indicates that polynucleotides and polypeptides corresponding to this gene are useful as a hormone for the diagnosis and treatment of endocrine disorders. The brain is a major site for secreting various hormones that regulate a wide range of body physiology. The secretory molecule encoded by this gene has very weak homology with FSH, and further indicates that it may serve as an endocrine. Endocrines can often be used in hormonal treatment of pathological disorders or change of physiology under certain circumstances such as in the treatment of reproductive disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1037 of SEQ ID NO:64, b is an integer of 15 to 1051, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 55

The translation product of this gene shares homology with a number of a C. elegans proteases, which are thought to be important in programmed cell death.

This gene is expressed primarily in activated T-cells and to a lesser extent in human stomach.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders or stomach diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:190 as residues: Lys-41 to Arg-47, Asp-125 to Lys-139, Ser-177 to Glu-185.

The tissue distribution in activated T-cells and stomach indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders, transplantation or stomach disease.

Particularly, the expression of the gene by activated T-cells can be used for the development of therapeutic agents as immune suppressants or immune modulators.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1168 of SEQ ID NO:65, b is an integer of 15 to 1182, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 56

The translation product of this gene shares sequence homology with CD53 tetraspan transmembrane molecule which is thought to be important in leukocyte activation. The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in KMH2 and activated T-cells, and to a lesser extent in tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infection, inflammation and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:191 as residues: Lys-99 to Arg-107.

The tissue distribution and homology to CD53 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and development of therapeutic agents for immune disorders including infection, allergy, inflammation, transplantation and immune deficiencies. Furthermore, expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:66, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

5 This gene is expressed primarily in fetal liver and to a lesser extent in neutrophils and keratinocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, autoimmune and skin defects. Similarly, polypeptides and  
10 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. liver, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum,  
15 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
20 NO:192 as residues: Pro-41 to Gln-50.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of inflammatory, general immune, and skin disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the  
25 diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in fetal liver, which is a primary site of definitive hematopoiesis. Expression of this gene product in neutrophils  
30 also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present  
35 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1091 of SEQ ID NO:67, b is an integer of 15 to 1105, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 58

This gene is expressed primarily in induced neutrophils.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and haemopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes  
15 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another  
20 tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the  
25 haemopoietic and immune systems. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
30 and/or immunotherapy targets for the above listed tissues. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
35 ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1265 of SEQ ID NO:68, b is an integer of 15 to 1279, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 59

10           This gene is expressed primarily in the endometrium.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of female infertility or reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, endometrium, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in endometrium indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product may show utility in the preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

35           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present

invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
5 a-b, where a is any integer between 1 to 1624 of SEQ ID NO:69, b is an integer of 15 to 1638, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 60

This gene is expressed primarily in the cells of the immune system, such as eosinophils, T-cells, dendritic cells, and tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as AIDS, inflammatory conditions, multiple myeloma, or SCID. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
20 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types or cell type (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
25 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in various immune cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the  
30 diagnosis and treatment of immune system disorders, such as AIDS. Furthermore, expression of this gene product in tonsils and other immune cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other  
35 processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility

as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product  
5 may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
10 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
15 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 873 of SEQ ID NO:70, b is an integer of 15 to 887, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

The translation product of this gene shares homology with human stannin, which is thought to play a role in the toxic effects of organotins. Moreover, the protein  
25 product of this gene may also show utility in the treatment, and/or prevention of a variety of defects in calcium regulation and metabolism.

This gene is expressed primarily in GM-CSF treated macrophages.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, particularly in the treatment or amelioration of aberrant immune response to tumor or foreign antigens, and in phagocytosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell  
35 type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, and cancerous and

wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:196 as residues: Gly-43 to Gly-55.

The tissue distribution in macrophages indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of immune disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or  
10 treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in macrophage also strongly indicates a role for this protein in immune function  
15 and immune surveillance. The protein product may even serve to stimulate the immune response, or may be used to inhibit such a response which may be useful during host versus graft disease or autoimmune disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.  
25 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 850 of SEQ ID NO:71, b is an integer of 15 to 864, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

30

## FEATURES OF PROTEIN ENCODED BY GENE NO: 62

This gene is expressed primarily in activated monocytes.

- 35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in monocytes indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and/or treating immune or hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1203 of SEQ ID NO:72, b is an integer of 15

to 1217, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:198 as residues: Met-1 to Gly-6.

The tissue distribution in monocytes indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and/or treating immune or hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in monocytes also strongly indicates a role for this protein in immune function and immune surveillance. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors

of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1703 of SEQ ID NO:73, b is an integer of 15 to 1717, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

When tested against K562 leukemia cell lines, supernatants removed from cells containing this gene activated the ISRE assay. Thus, it is likely that this gene activates  
20 leukemia cells through the Jak-STAT signal transduction pathway. The interferon-sensitive response element is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE  
25 element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in spleen from a chronic lymphocytic leukemia  
30 patient.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly leukemias. Similarly,  
35 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system,

expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. spleen, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in leukemia cells combined with the detected ISRE biological activity in K562 cell lines indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of chronic lymphocytic leukemia. Furthermore, since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 1262 of SEQ ID NO:74, b is an integer of 15 to 1276, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 65

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
15 of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
20 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neutrophils inactivation and other immune system disorders. Furthermore,  
25 polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune  
30 function and immune surveillance. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as  
35 as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease,

scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1130 of SEQ ID NO:75, b is an integer of 15 to 1144, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 66**

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly neutropenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune system disorders. Furthermore, expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune

surveillance. The protein may also be useful in the inhibition of neutrophil activation which may show utility in host-versus-graft disease and autoimmune disorders. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid  
5 arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug  
10 induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy  
15 targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
20 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 904 of SEQ ID NO:76, b is an integer of 15 to 918, where both a and b correspond to the positions of nucleotide residues shown in  
25 SEQ ID NO:76, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 67**

30 When tested against U937 myeloid cell lines, supernatants removed from cells containing this gene activated the GAS promoter element. Thus, it is likely that this gene activates myeloid cells, and their progenitors, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-  
35 STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by

the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as neutropenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a  
10 number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a  
15 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:202 as residues: Asp-23 to Trp-29.

The tissue distribution in neutrophils, combined with the detected GAS  
20 biological activity in myeloid cell lines indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune system disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells  
25 and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. The protein product of this gene may show utility in the inhibition of neutrophil activation which may show utility in host-versus-graft disease and in  
30 autoimmune disorders. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as  
35 host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease,

scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1051 of SEQ ID NO:77, b is an integer of 15 to 1065, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

This gene is expressed primarily in neutrophils induced with IL-1 and LPS.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as neutropenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of inactive immune response to foreign antigens. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for

the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in neutrophils also strongly indicates a role for this protein in

5 immune function and immune surveillance. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and

10 tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood

15 lineages, and in the differentiation and/or proliferation of various cell types. The protein product of this gene may also show utility in the inactivation of neutrophils which may show utility in host-versus-graft disease or in autoimmune disorders, for example. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

25 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:78, b is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

The translation product of this nucleotide sequence shares homology with a

35 number of cysteine proteinases. Contact of cells with supernatant expressing the product of this gene increases the permeability of TF-1 Myeloid cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that

is initiated when the product of this gene binds a receptor on the surface of the myeloid cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating myeloid cells.

This gene is expressed primarily in tissue from an ovarian tumor.

5           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive disorders, particularly ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, immune, hematopoietic, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum,  
15 amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The homology to proteins of the cysteine proteinase family, tissue distribution  
20 in ovarian tissues, combined with the detected calcium flux activity in myeloid cells indicates that the protein product of this gene may show utility in the treatment, and/or prevention of a variety of reproductive disorders, such as in ovarian cancer, or even in the modulation of the immune response to. Thus, it is useful for diagnosis and treatment of ovarian cancer. Furthermore, the biological activity data, when compared  
25 to the tissue distribution, suggest that the translation product of this gene could be useful in activating the immune system to respond to cancerous growths, particularly those involving ovarian cancer. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

30           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35           Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 970 of SEQ ID NO:79, b is an integer of 15 to

984, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 70

This gene is expressed primarily in anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as autoimmune disorders including lupus. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:205 as residues: Ser-26 to Lys-34.

The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-

host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed  
5 progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
10 ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
15 a-b, where a is any integer between 1 to 1233 of SEQ ID NO:80, b is an integer of 15 to 1247, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 71

This gene shares homology with the human adult heart neutral calponin, which is implicated in the regulation and modulation of smooth muscle contraction. It is capable of binding to actin, calmodulin, troponin C, and tropomyosin. The interaction  
25 of calponin with actin inhibits the actomyosin Mg-ATPase activity. Therefore, the protein product of this gene may be beneficial as a vasoconstrictor or vasodilator, a muscle relaxor, treatment for tetanus stimuli, or for the treatment of various cardiovascular disorders. The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as  
30 a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in adrenal gland tumor and human 12 week embryo. Furthermore, the gene is expressed in cardiomyopathy tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
35 biological sample and for diagnosis of diseases and disorders: endocrine, developmental, cardiovascular disorders, particularly diseases involving abnormal cellular proliferation such as cancers particularly of the adrenal gland, and disorders

involving heart muscle, such as cardiomyopathy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adrenal gland, heart, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. heart, muscle, endocrine, developmental, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of abnormal cellular proliferation, such as tumors. Alternatively, given the tissue distribution and the homology to human adult heart neutral calponin, it indicates that the translation product of this gene is useful for detecting, identifying, and/or treating disorders involving the degeneration of the regulation and modulation of smooth muscle contraction, such as is seen with cardiomyopathies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 932 of SEQ ID NO:81, b is an integer of 15 to 946, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 72

This gene is expressed primarily in human bone and 9 week embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, skeletal, immune, hemopoietic, or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematoplastic tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, bone, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:207 as residues: Ala-22 to Lys-36.

The tissue distribution in bone and embryonic tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or the treatment of hemopoietic diseases. Furthermore, it may be useful in influencing bone mass in such conditions as osteoporosis. More generally, this gene may play a role in the survival, proliferation, and/or differentiation of hematopoietic cells in general, and may be of use in augmentation of the numbers of stem cells and committed progenitors.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1378 of SEQ ID NO:82, b is an integer of 15 to 1392, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 73**

This gene is expressed primarily in T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorder of the immune or hematopoietic systems, particularly immunodeficiencies or inflammatory conditions, such as AIDS, SCID, leukemias, or multiple myeloma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:208 as residues: Asp-26 to Leu-36, Leu-42 to Phe-50.

The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of disorders of the immune system such as AIDS. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 1141 of SEQ ID NO:83, b is an integer of 15 to 1155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 74

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, including progenitors, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

DVLLPLL YLLVRKHINRAGIGNTFQGGANCI (SEQ ID NO:345), MCCCLCCT  
 SWSGSTSTERVSGTRFREVPTASCSSSAPAPSELGSSLSVAAAALLSLPPRARLA  
 LPRLPRL PSQENLRNPKGPQGNFQAPGAFVLSSSVA (SEQ ID NO:346), CAAA  
 SAVPPGPEAHQQSGYREHVSGRCQLHHVRPLHPRRPNSALLSLLLLLLFSASH  
 QEPGWHSQGSRAF QARRISGIPRDPRGTSKHLELLSFLVLWHRCCLPGG RXF  
 CESLXQGRSACLLHQKPPLMLLSAPLGEQLP TQLLLPPRSSGSKFXRYQRPGP  
 RVGVHLHKGSSEIREAGGPQLWPQC PHPVDLDVLR TTQHCLQSEGPTS VH  
 LSSV (SEQ ID NO:347), EVEEAELAAALPMEPRASIAGASGAADMHFPCPAXGTH  
 RXA YPQEGSTYATELERTKAPGAWKFPWGPLGFLRFSWLGRRGSLGSAS  
 RALGGRLRRAAAATEREEPSSDGA GAEDEHDAVGTS LKRVPDTRS VDVLPD  
 QEVQQRQQHI (SEQ ID NO:348), RRISGIPRDPRGTSKHLELLSFLVLWHRCCL  
 (SEQ ID NO:349), and/or RTKAPGAWKFPWGPLGFLRFSWLGRRGSL (SEQ ID  
 NO:350). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of smooth muscle tissue, particularly vascular disorders, such as vasculitis, microvascular disease, atherosclerosis, stroke, aneurysm, and

35

embolism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of smooth muscle tissue, expression of this gene at significantly higher or lower levels  
 5 may be routinely detected in certain tissues and cell types (e.g. smooth muscle, vascular, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the  
 10 disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:209 as residues: Ser-23 to Glu-54.

The tissue distribution in smooth muscle, combined with the detected GAS biological activity indicates that polynucleotides and polypeptides corresponding to this  
 15 gene are useful for diagnosis and treatment of vascular or cardiopulmonary disorders. In addition, the protein may show utility in the modulation of the immune system in response to various vascular disorders, particularly in the early stages of atherosclerosis, embolism, thrombosis, and stroke. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy  
 20 targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
 25 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:84, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide residues shown  
 30 in SEQ ID NO:84, and where b is greater than or equal to a + 14.

## **FEATURES OF PROTEIN ENCODED BY GENE NO: 75.**

35 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PRLAQLRLLSL (SEQ ID NO:351),  
 QSDFREMNTNSTSNAAKAREAAQQGRGRD REAIFSSSALEHLVCYLQAYKHT

LLFIRSLNEHGLQQLLFQWRDGLFGNWFYFRIPILLFFTGFHCYHLSC PHLPC  
 AQRQSSRGTVPYVLCPPHHLHHYSWFPFLIPVLHTLPKLQPKFHGRPEQPL  
 NLLQVKPTSGTI ASAEQVWVK (SEQ ID NO:352). VCYLQAYKHTLLFIRSLNEH  
 GLQQLLFQW (SEQ ID NO:353), and/or VPYVLCPPHHLHHYSWFPFLIPVLH  
 5 TLPKL (SEQ ID NO:354). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention. The gene encoding the disclosed cDNA is believed to  
 reside on chromosome 1. Accordingly, polynucleotides related to this invention are  
 useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in brain, ulcerative colitis, pancreas tumor,  
 10 placenta, and to a lesser extent, in thyroid, bone marrow stromal cells, B-cell  
 lymphoma, and hemangiopericytoma.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 15 not limited to, tumors and degenerative conditions involving infiltration by the immune  
 system, particularly in soft-tissues, in addition to, neural, gastrointestinal, metabolic,  
 reproductive, endocrine, and hematopoietic, or immune disorders. Similarly,  
 polypeptides and antibodies directed to these polypeptides are useful in providing  
 immunological probes for differential identification of the tissue(s) or cell type(s). For a  
 20 number of disorders of the above tissues or cells, particularly of the immune system,  
 expression of this gene at significantly higher or lower levels may be routinely detected  
 in certain tissues and cell types (e.g. neural, gastrointestinal, metabolic, reproductive,  
 endocrine, hematopoietic, immune disorders, and cancerous and wounded tissues) or  
 bodily fluids (e.g. lymph, serum, bile, amniotic fluid, plasma, urine, synovial fluid and  
 25 spinal fluid) or another tissue or cell sample taken from an individual having such a  
 disorder, relative to the standard gene expression level, i.e., the expression level in  
 healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:210 as residues: Lys-33 to Arg-51, Gly-64 to Gly-74.

30 The tissue distribution in brain tissues indicates that polynucleotides and  
 polypeptides corresponding to this gene are useful for treating the secondary effects of  
 immune system involvement in diseases such as pancreatic tumors, ulcerative colitis,  
 and Alzheimer's disease. Protein, as well as, antibodies directed against the protein may  
 show utility as a tumor marker and/or immunotherapy targets for the above listed  
 35 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
 and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more
- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1244 of SEQ ID NO:85, b is an integer of 15 to 1258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 76**

- When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter
- 15 element. Thus, it is likely that this gene activates sensory neuron cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the
- 20 following amino acid sequence: ESERAVVYLITGALFIVSSCVLCFLPSSRRE (SEQ ID NO:355). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

- 25 This gene is expressed primarily in activated T cells, tonsils, and activated monocytes.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
- 30 not limited to, immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the activated T cells, tonsils and activated monocytes, expression of this gene at significantly higher or lower levels may be
- 35 routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in T-cells and immune tissues or cell types, combined  
5 with the detected EGR biological activity indicates that polynucleotides and  
polypeptides corresponding to this gene are useful for diagnosis and treatment of  
immune and inflammatory disorders. Moreover, this gene product may be involved in  
the regulation of cytokine production, antigen presentation, or other processes that may  
also suggest a usefulness in the treatment of cancer (e.g. by boosting immune  
10 responses). Since the gene is expressed in cells of lymphoid origin, the natural gene  
product may be involved in immune functions. Therefore it may be also used as an  
agent for immunological disorders including arthritis, asthma, immunodeficiency  
diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease,  
inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis,  
15 hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to  
transplanted organs and tissues, such as host-versus-graft and graft-versus-host  
diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue  
injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia,  
rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene  
20 product may have commercial utility in the expansion of stem cells and committed  
progenitors of various blood lineages, and in the differentiation and/or proliferation of  
various cell types. Protein, as well as, antibodies directed against the protein may show  
utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
25 and accessible through sequence databases. Some of these sequences are related to SEQ  
ID NO:86 and may have been publicly available prior to conception of the present  
invention. Preferably, such related polynucleotides are specifically excluded from the  
scope of the present invention. To list every related sequence is cumbersome.  
Accordingly, preferably excluded from the present invention are one or more  
30 polynucleotides comprising a nucleotide sequence described by the general formula of  
a-b, where a is any integer between 1 to 1304 of SEQ ID NO:86, b is an integer of 15  
to 1318, where both a and b correspond to the positions of nucleotide residues shown  
in SEQ ID NO:86, and where b is greater than or equal to a + 14.

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#### FEATURES OF PROTEIN ENCODED BY GENE NO: 77

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

10 This gene is expressed primarily in eosinophils and activated T-cells and to a lesser extent in lung and thymus stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:212 as residues: Met-1 to Trp-10.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders, including infection, allergy, inflammation, graft rejection and immunodeficiency. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in T cells and eosinophils also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 964 of SEQ ID NO:87, b is an integer of 15 to 978, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 78

One embodiment of this gene comprises polypeptides of the following amino acid sequence:  
 MWVXGEEVLGSHAASPAFLHRCFSEESCVSIPVEGYVVVLQPDAPQILLSGTA  
 HFARPAVD FEGTNGVPLFPDLQITCSISHQVEAKKDESWQGTVTDT RMSDEIVH  
 NLDGCEISLVGDDLDPERESLLD TTS LQQRGLELTNTSAYLTIAGVESITVYEEI  
 LRQARYRLRHGAALYTRKFRLSCSEMNGRYS SNEFIVEVNV LHSMNRVAHPS  
 HVL SXQQFLHRGHQPPPEMAGHSLASSHRNSST (SEQ ID NO:356), LGSHAA  
 SPAFLHRCFSEESC VSI (SEQ ID NO:357), GYVVVLQPDAPQILLSGTAHFARP  
 AVDFE (SEQ ID NO:358), ITCSISHQVEAKKDESWQGTVTDT RM (SEQ ID  
 NO:359), NLDGCEISLVGDDLDPERESLLD TTS LQ (SEQ ID NO:360), SAYLTI  
 AGVESITVYEEILRQAR (SEQ ID NO:361), RLSCSEMNGRYS SNEFIVEVNV LH  
 SM (SEQ ID NO:362), and/or QQFLHRGHQPPPEMAGHSLASSHRN (SEQ ID  
 NO:363). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in brain and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain afflictions such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders, as well as immune disorders such as leukemias, lymphomas, AIDS, arthritis and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:213 as residues: Gly-36 to Leu-44.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of developmental, degenerative and behavioral diseases and conditions of the brain such as aphasia, depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, specific brain tumors, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. In addition, the expression in spleen would suggest a possible role in the detection and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders as well as conditions of general microbial infection, inflammation or cancer.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1849 of SEQ ID NO:88, b is an integer of 15 to 1863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 79

When tested against K562 leukemia cell lines, supernatants removed from cells containing this gene activated the ISRE assay. Thus, it is likely that this gene activates

leukemia cells through the Jak-STAT signal transduction pathway. The interferon-sensitive response element is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

- 5 Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. One embodiment of this gene comprises polypeptides of the following amino acid sequence: MADSETFISLE  
 ECRGHKRARKRTSMETALALEKLFPKQCQVLGIVTPGIVVXPMGSGSNRPQEI  
 10 EIGESGFALLFPQIEGI KIQPFHFIKDPKNLTLEHQLTEVGLLDNPELRVVLV  
 FGYNCKVGASNYLQQVVSTFSDMNILAGGQV DNLSSLTSEKNPLDID AS  
 GVVGLSFSGHRIQSATVLLNEDVSDEKTAEAAMQRLKAANIPEHNTIGFMFA  
 CVGRGFQYYRAKGNVEADAFRKFFPSVPLFGFFGNGEIGCDRIVTGNFILRKC  
 NEVKDDDLFHSYTTIMA LIHLGSSK (SEQ ID NO:364), HKRARKRTSMETAL  
 15 ALEKLFP (SEQ ID NO:365), MGSGSNRPQEI EIGESGFALLFPQ (SEQ ID  
 NO:366), FHFIKDPKNLTLEHQLTEVGL (SEQ ID NO:367), FGYNCKVGASN  
 YLQQVVSTFSD (SEQ ID NO:368), TSEKNPLDIDASGVVGLSFS (SEQ ID  
 NO:369), NEDVSDEKTAEAAMQRLKAANIPEHN (SEQ ID NO:370), YYRAKGNV  
 EADAFRKFFPSVPLFGF (SEQ ID NO:371), and/or IGCDRIVTGNFILRKCNE  
 20 VKDDDLFH (SEQ ID NO:372). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in endothelial cells and to a lesser extent in reproductive and various endocrine organs.

- 25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, cardiovascular and immune defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 30 of the above tissues or cells, particularly of the immune, cardiovascular, and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. endothelial, reproductive, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual  
 35 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:214 as residues: Ser-44 to Ala-50.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer, cardiovascular and reproductive disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:89, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 80**

This gene is expressed primarily in human tongue and TNF-induced epithelium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, mucosal, oral, and inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of mucosal and epidermal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. tongue, epithelial, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:215 as residues: Ser-39 to Leu-48, Ala-65 to Pro-75, Pro-81 to Cys-87.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of disorders of the oral and intestinal mucosa, inflammation and other epithelial disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 877 of SEQ ID NO:90, b is an integer of 15 to 891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 81**

This gene is expressed primarily in activated neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, autoimmune, and inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a  
25 number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
30 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis and treatment of immune, autoimmune, and inflammatory disorders. Furthermore, this gene product may be  
35 involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin,

the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in neutrophils strongly indicates a role for this protein in immune function and immune surveillance.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1960 of SEQ ID NO:91, b is an integer of 15 to 1974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 82

- 20 This gene is expressed primarily in primary dendritic cells, and to a lesser extent in neutrophils, monocytes, and osteoblasts.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic conditions. Similarly, polypeptides and
- 25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, cancerous and wounded tissues) or bodily
- 30 fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- Preferred epitopes include those comprising a sequence shown in SEQ ID
- 35 NO:217 as residues: Gly-47 to Arg-53.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of immune,

inflammatory and hematopoietic disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in neutrophils and primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1409 of SEQ ID NO:92, b is an integer of 15 to 1423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 83

One embodiment of this gene comprises polypeptides of the following amino acid sequence:

MPKRKVTFGVGDEEDEDEIIVPKKKLVDPVAGSGGPGSRFKGKHSLSDEEE  
 DDDGGSSKYDILASEDVEGQEAATLPSEGGVRITPFNLQEEMEEGHFDADGN  
 YFLNRDAQIRDSWLDNIDWVKIRERPPGQRQASDSEEDSLGQTSMSAQALLEG  
 LLELLLPRETVAGALRRLGARGGGKGRKGPQPSSPQRLDRLSGLADQMVAR  
 GNLG VYQETRERLAMRLKGLGCQTLGPHNPTPPPSLDMFAEELAELEELETPTPT  
 QRGAEASRGDGLVDVMWEYKWENTGDAELYGPFTSAQMQTWVSEGYFPDGV  
 YCRKLDPPGGQFYNSKRIDFDLYT (SEQ ID NO:373), TFQGVGDEEDEDEIIVP  
 KKKLVDP (SEQ ID NO:374), PGSRFKGKHSLSDEEEDDDGGSSKY (SEQ ID  
 NO:375), EAATLPSEGGVRITPFNLQEEMEEG (SEQ ID NO:376), FLNRDAQIRDS  
 WLDNIDWVKIRERPPGQR (SEQ ID NO:377), SLGQTSMSAQALLEG LLELL  
 PRETV (SEQ ID NO:378), RGGGKGRKGPQPSSPQRLDRLSGLADQ (SEQ ID  
 NO:379), QETRERLAMRLKGLGCQTLGPHNP (SEQ ID NO:380), DMFAEELAEEL  
 LETPTPTQRGAEASRGD (SEQ ID NO:381), and/or ELYGPFTSAQMQTW

VSEGYFPDGVYCRKLD (SEQ ID NO:382). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in fetal lung, stromal cells and lymphoma cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic and respiratory disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a  
10 number of disorders of the above tissues or cells, particularly of the haemopoietic and respiratory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. lung, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder,  
15 relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:218 as residues: Met-1 to Trp-15, Thr-52 to Met-58.

The tissue distribution indicates that polynucleotides and polypeptides  
20 corresponding to this gene are useful for the treatment and diagnosis of diseases of the haemopoietic and respiratory systems. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
25 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
30 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1351 of SEQ ID NO:93, b is an integer of 15 to 1365, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

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#### FEATURES OF PROTEIN ENCODED BY GENE NO: 84

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PHSSRVSFQLQSLSF (SEQ ID NO:383), RGQPRPCVSGVCLS PHSRFWECCSFYLQGLPALRCSRTPPGCHFFRVFPSCPFSSSRSPSCFT HICPV  
 5 VRIQFSRALWVSTCLVLAITPGKWLLPEDRALSLMLLASLQCCPPFPGAWWMQ VLTHKGRQAGLG PGVSSRPL (SEQ ID NO:384, S NIKSLPPTNSLSLLRA QTGTDCAVSPGLAGPCHQRGLEDTPGPRPACLPLCVSTCIHQAPKGGGQHWRE  
 EA SSIRDRAISSGRSHFPGVMAKTKHVDTHNARENWIRTTGQMWVKHEG EREEEKGHEGKTLKK (SEQ ID NO:385), VCLSPHSRFWECCSFYLQGLPALRC  
 10 (SEQ ID NO:386), QFSRALWVSTCLVLAITPGKWLLPEDR (SEQ ID NO:387), SLSLLRAQTGTDCAVSPGLAGPCHQRG (SEQ ID NO:388), and/or SGRSHFPG VMAKTKHVDTHNARENWIRT (SEQ ID NO:389). Polynucleotides encoding these polypeptides are also encompassed by the invention. When tested against U937 cell  
 lines, supernatants removed from cells containing this gene activated the GAS (gamma  
 15 activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the Jak-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-  
 20 STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in T-cells and lungs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 25 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, respiratory and immune diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and respiratory systems,  
 30 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. pulmonary, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
 35 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:219 as residues: His-38 to Ala-43.

The tissue distribution in T-cells and lung tissue, combined with the detected GAS biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the respiratory and immune systems. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The protein may show utility in modulating the immune response to various pulmonary disorders or conditions, particularly in emphysema, or ARDS.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 742 of SEQ ID NO:94, b is an integer of 15 to 756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 85

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARVEVQGGPGAKVDAGEGQ (SEQ ID NO:390), WVVL  
 5 SQLQA QGVAGMMCSYPEGQKKGKEATRSHRWVPRSLPGMGSLAAPH  
 NPWLAPLALLEIPXPVLCEWKRKLIAL EEVSECRPGVGGGGGFLSXCRR  
 GHLSFLSGAPYPLFPISPLX (SEQ ID NO:391), ELRHGGPRQVKDSFLDYM  
 GYPDEDRA GPPSRWFPRERFLSPPTV VPLCVELRLGFESGMGWGVPGSSHS  
 EGGPEARWPLIAPMYTVTQWFQRPNSGRGPQPPQXRGEIGKRGY GAPER  
 10 KLRWPLLXWERXPPPPTPGRHSETSSSAISFLFHSQRTGWGISSSANGASQGL  
 LWGAARXLPIP GRDLGTHLWDLVASFPFFCPSG (SEQ ID NO:392), PEGQKK  
 GKEATRSHRWVPRSLPGM (SEQ ID NO:393), LRLGFESGMGWGVPGSSHSEG  
 GPEAR (SEQ ID NO:394), and/or HSQRTGWGISSSANGASQGLLWGA (SEQ ID  
 NO:395). Polynucleotides encoding these polypeptides are also encompassed by the  
 15 invention.

This gene is expressed primarily in eosinophils, dendritic cells, Jurkat cells and tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, or hematopoietic disorders, particularly inflammatory, autoimmune, allergy, and hypersensitivity conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 25 of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
 30 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in a variety of immune and hematopoietic-specific cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for modifying the response of the immune system in autoimmune diseases  
 35 and inflammatory conditions. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or

leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behaviour. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:95, b is an integer of 15 to 938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

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#### FEATURES OF PROTEIN ENCODED BY GENE NO: 86

This gene is expressed primarily in cells from fibrosarcoma tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscle, or endothelial disorders, particularly fibrosarcomas and fibroids. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeleto-muscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. skeleto-muscular, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fibrosarcoma tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various muscle disorders, in particular fibrosarcomas. In addition, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). The gene or protein product of this gene may also show utility in modulating the immune response to proliferative tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 914 of SEQ ID NO:96, b is an integer of 15 to 928, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

5           This gene is expressed primarily in helper T-Cells, cerebellum, and to a lesser extent, in mesangial cells, fetal lung, fetal liver, cortex, and adipose tissue.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
10   not limited to, immune, or neural disorders, particularly, for modulation of immune responses to viral or bacterial infections, or neurodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of  
15   this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. renal, developmental, pulmonary, hepatic, neural, metabolic, immune, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
20   expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in helper T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for modifying the immune response to foreign agents such as bacteria or virus. In addition, this gene product may be  
25   involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma,  
30   immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue  
35   injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed

progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, based upon the expression within the cerebellum and cortex, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1701 of SEQ ID NO:97, b is an integer of 15 to 1715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 88

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates promyelocytic cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many

genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

FIMKLLYQLMLTTSSSYSLITHLCYSIFLCSFYFHFPCNVSLFVLISEEFIYD  
(SEQ ID NO:396), LMLTTSSSYSLITHLCYSIFL (SEQ ID NO:397), LCSFYFH  
FPCNVSLFVLISEE (SEQ ID NO:398), MRKNIFAILDKMLTCLINELFRNQYKET  
10 NITREVKIKGTEENGIAQMSYKAI (SEQ ID NO:399), DKMLTCLINELFRNQ  
YKETN (SEQ ID NO:400), and/or NITREVKIKGTEENGIAQMSY (SEQ ID  
NO:401). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal lung.

15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes  
20 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developmental and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Pulmonary, developmental, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, pulmonary surfactant or sputum,  
25 amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene only in fetal lung, combined with the  
30 detected GAS biological activity indicates that it plays a key role in development of the pulmonary system. This would suggest that misregulation of the expression of this protein product in the adult could lead to lymphoma or sarcoma formation, particularly in the lung. It may also be involved in the predisposition to certain pulmonary defects such as pulmonary edema and embolism, bronchitis and cystic fibrosis. Moreover, the  
35 protein product of this gene may be beneficial in the treatment of underdeveloped lung tissue, as exists in premature infants, both through the use of antibodies directed against the protein, through a gene therapy-based regime, or through the action of the protein

itself, either directly or indirectly. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:98, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 89**

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element.  
20 Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the Jak-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the  
25 binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GISERKP (SEQ ID NO:402). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural or immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
35 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues

or cell types (e.g. neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:224 as residues: Ile-40 to Trp-50.

The tissue distribution in brain combined with the detected GAS biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of central nervous system disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, the protein may show utility in modulating the immune response to various neurodegenerative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1527 of SEQ ID NO:99, b is an integer of 15

to 1541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 90

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QSPAVSYTVTSQVPWGLGLLAGEKR (SEQ ID NO:403), LPSHPLRPLTFS SAMCMHLPPPLCRRALSAPFATQHRPWSVAAACLPRIHQN  
 10 PLDAEYPSGCCRMSFLPAACSNISQECH YTLMSHSEASTLQXAQLL (SEQ ID NO:404), MLLQAAGRKLMRQPDGYSASRGFWWMRGRQAAATLHGRCWVA KGADSAAL RQRGGGRCMHIADEKVRGLSGCDGS (SEQ ID NO:405), LCRRA ALSAPFATQHRPWSVAAACL (SEQ ID NO:406), RGFWWMRGRQAAATLHGR CWVAKG (SEQ ID NO:407), and/or QRGGGRCMHIADEKVRGLSGCDG (SEQ ID  
 15 NO:408). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammatory and immune conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene  
 25 at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 30 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:225 as residues: Pro-34 to His-39, Pro-44 to His-54.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis, and  
 35 treatment of inflammatory, general immune, and infectious diseases. Moreover, the expression of this gene indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem

cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 867 of SEQ ID NO:100, b is an integer of 15 to 881, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

### **30 FEATURES OF PROTEIN ENCODED BY GENE NO: 91**

When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In addition, contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of stromal cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both stromal, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating stromal cells. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

THPSHSIVIQSTVSLCLTASSRRKKSDCLSLCQVSCSQRPGRSHKTNVAWGFLM  
SRVHFSVRWVSGGRI TGAICKESSLPCKEIQKGKACYFCHHPAQQSTPFHSI  
(SEQ ID NO:409, VIQSTVSLCLTASSRRKKSDCLSLCQV (SEQ ID NO:410),  
and/or ICKESSLPCKEIQKGKACYFCHHPAQQ (SEQ ID NO:411). Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils, and to a lesser extent, in cord blood.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or developmental disorders, particularly inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hemopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, developmental, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:226 as residues: Glu-32 to Arg-37.

The tissue distribution in neutrophils, combined with the detected GAS and calcium flux biological activities, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study and treatment of inflammatory, infectious, and hemopoietic disorders. Similarly, expression within cord blood  
5 indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders, particularly of the developing hematopoietic system. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could  
10 again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
15 ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  
20 a-b, where a is any integer between 1 to 933 of SEQ ID NO:101, b is an integer of 15 to 947, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The gene encoding the disclosed cDNA is thought to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

30 This gene is expressed primarily in macrophages, T cells, dendritic cells, testes and pancreas tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
35 not limited to, immune disorders including testis and pancreas tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a

number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:227 as residues: Gln-85 to Lys-91, Pro-106 to Ser-117, Pro-124 to Ala-130, Trp-154 to Trp-160.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders such as testes and pancreas tumors. Furthermore, polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in T cells and primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus; drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1355 of SEQ ID NO:102, b is an integer of 15 to 1369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 93

10           This gene is expressed primarily in brain tissue from a patient suffering from manic depression.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly manic depression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25           The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis of manic depression and other disorders of the CNS. Furthermore, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function.

35           Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of

developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10         Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1217 of SEQ ID NO:103, b is an integer of 15 to 1231, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

This gene is expressed primarily in anergic T-cells.

- 20           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly autoimmune disorders such as lupus. Similarly, polypeptides and antibodies directed to these polypeptides are
- 25          useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine,
- 30          synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution in T-cells indicates that polynucleotides and polypeptides
- 35          corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Moreover, the protein product of this gene may play a role in the regulation of the proliferation; survival; differentiation; and/or activation of

potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1228 of SEQ ID NO:104, b is an integer of 15 to 1242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 95

This gene is expressed primarily in the spinal cord.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, neural disorders, particularly CNS, PNS, and a variety of congenital malformations of the spinal column and injuries of the spinal cord. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. CNS, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:230 as residues: Ser-44 to His-52.

The tissue distribution in spinal cord tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the brain and nervous system. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1137 of SEQ ID NO:105, b is an integer of 15 to 1151, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 96**

This gene is expressed primarily in smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscular, vascular, or cardiopulmonary disorders, particularly a variety of diseases that include wasting and muscle mass loss including amyotrophic lateral sclerosis, embolism, atherosclerosis, stroke, and aneurysm. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neuromuscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. muscle, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:231 as residues: Leu-37 to Trp-44.

The tissue distribution in smooth muscle indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various muscle disorders, such as muscular dystrophy, cardiomyopathy, fibroids, myomas, vascular disorders, and rhabdomyosarcomas. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1614 of SEQ ID NO:106, b is an integer of 15 to 1628, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

35

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 97

This gene is expressed primarily in the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the brain and central nervous system, such as Alzheimer's disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. brain, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered bahaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1451 of SEQ ID NO:107, b is an integer of 15 to 1465, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 98

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SLQVLRTLGSKCGDFLRSRFCKDVLPKLAGSLVT QAPISARAGPVYSHTLAFKLQLAVLQGLGPLCERLDLGEGDLNKVADACLIYLS VKQPVKLQEAARSVFL HLMKVDPDSTWFLNLNELYCPVQFTPPHPSLHPVQLX GASGQQNPXHDQRAPAAQGAAVTLLPHHRGHRSL PYCQPEAGLTTPRP (SEQ ID NO:412), GADGNVSDFDNEEEEQSVPPKVDENDTRPDVEPPLPLQIQIAM DVMERCIHLLSDKNLQIRLKVLDVLDL CVVVLQSHKNQLLPLAHQAWPSL VHRLTRDAPLAVLRAFKFYVPWEASVVTTFFAAGSAKMSCQSWLAP (SEQ ID NO:413), TLGSKCGDFLRSRFCKDVLPKLAGSL (SEQ ID NO:414), PVYSHTL AFKLQLAVLQGLGPLCERLDLG (SEQ ID NO:415), SVPPKVDENDTRPDV EPPLPLQIQIAM (SEQ ID NO:416), and/or WPSLVHRLTRDAPLAVLRAFK FYVPW (SEQ ID NO:417). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in kidney cortex, hemangiopericytoma, fetal spleen, infant brain, and to a lesser extent, in pancreas, lymph node, fetal liver, ovarian tumor, T-cells and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal, immune, neural, or developmental disorders, particularly tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. renal, immune, neural, developmental, reproductive, ovarian, hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:233 as residues: Pro-24 to Pro-37.

The tissue distribution in proliferating tissues and cells, combined with its distribution in developing tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating tumors. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1251 of SEQ ID NO:108, b is an integer of 15 to 1265, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 99**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SLGISTFGIMVFSVYFGGIMISIPYSGISFGNKKELNID SCYNMVNLKNIMFSERSQT (SEQ ID NO:418), HASGNNNDPLWFLTYL (SEQ ID NO:419), MVFSVYFGGIMISIPYSGISF (SEQ ID NO:420), and/or FGNKKELNID SCYNMVNLKN (SEQ ID NO:421). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in T-cells, spleen, and pancreas.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, endocrine, pancreatic, cancerous and wounded

tissues) or bodily fluids (e.g.lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:234 as residues: Thr-24 to Arg-29.

The tissue distribution of this gene predominantly in cell types or tissues associated with the immune system indicates that the gene could be important for the treatment or detection of immune or hematopoietic disorders including, but not limited to, arthritis, asthma, immunodeficiency diseases and leukemia. Moreover, the expression within pancreatic tissues indicates that the protein product of this gene may be useful in the treatment or prevention of a variety of metabolic disorders, such as diabetes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:109 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

20 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 992 of SEQ ID NO:109, b is an integer of 15 to 1006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 100**

The gene encoding the disclosed cDNA is believed to reside on the X chromosome. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for the X chromosome.

This gene is expressed primarily in urinary bladder carcinoma HSC172 cells, and to a lesser extent, in human adult heart, lung, osteoclastoma, and liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, urogenital, or renal disorders, particularly urinary bladder carcinoma and

other cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bladder, expression of this gene at significantly higher or lower levels may be  
5 routinely detected in certain tissues or cell types (e.g. renal, cardiopulmonary, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the  
10 disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:235 as residues: Gly-18 to Lys-23, Pro-31 to Gly-38.

The tissue distribution in urinary bladder carcinoma indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis  
15 and therapeutic targeting of urinary bladder carcinoma, osteoclastoma, and other cancers. Additionally, the tissue distribution in heart, lung and osteocarcinoma indicates an indication for the use of this gene and gene product in diagnosis and treatment of disorders in the heart and lung. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above  
20 listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:110 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
25 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1244 of SEQ ID NO:110, b is an integer of 15 to 1258, where both a and b correspond to the positions of nucleotide residues shown  
30 in SEQ ID NO:110, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 101

35 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

MNSFSVIASIVVLLPFPGLSVSACLPSHSHQCKTFILLFLPSSEKTLXXXPP

SHSSTLGGQGGQIMRSGDRXHXG (SEQ ID NO:422), VVFFXXFFEMESH  
 SVAQAGVQWRNLGSLQAL PPGFMPFSCLSLPGSWDYRRPPPSPANLXCIF  
 SRDGGHHVSQXGLDLLTS (SEQ ID NO:423), IVVLLPFPGLSVSACLPS  
 HSHQCKTFIL (SEQ ID NO:424), and/or PGFMPFSCLSLPGSWDYRRPPPSPAN  
 5 (SEQ ID NO:425). Polynucleotides encoding these polypeptides are also encompassed  
 by the invention.

This gene is expressed primarily in adipose tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 10 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, obesity and other metabolic disorders. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological probes  
 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the endocrine system, expression of this  
 15 gene at significantly higher or lower levels may be routinely detected in certain tissues  
 or cell types (e.g. adipose, metabolic, neural, and cancerous and wounded tissues) or  
 bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or  
 another tissue or cell sample taken from an individual having such a disorder, relative to  
 the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 20 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:236 as residues: Arg-28 to Asn-33.

The tissue distribution in adipose tissue indicates that polynucleotides and  
 polypeptides corresponding to this gene are useful for the treatment of obesity and other  
 25 metabolic and endocrine conditions or disorders. Furthermore, the protein product of  
 this gene may show utility in ameliorating conditions which occur secondary to aberrant  
 fatty-acid metabolism (e.g. aberrant myelin sheath development), either directly or  
 indirectly. Protein, as well as, antibodies directed against the protein may show utility  
 as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available  
 and accessible through sequence databases. Some of these sequences are related to SEQ  
 ID NO:111 and may have been publicly available prior to conception of the present  
 invention. Preferably, such related polynucleotides are specifically excluded from the  
 scope of the present invention. To list every related sequence is cumbersome.  
 35 Accordingly, preferably excluded from the present invention are one or more  
 polynucleotides comprising a nucleotide sequence described by the general formula of  
 a-b, where a is any integer between 1 to 1439 of SEQ ID NO:111, b is an integer of 15

to 1453, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 102

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: YRFKNPKCRLFSVPCR (SEQ ID NO:426), TQNRELLAWK PKGTDDICTSHNTTHIQKMPGE ANSCCPRGAKSYHIDCWPPALFPRCVAYLFL  
 10 NKPATLRKKYYCKPYHTQLHPAWHREKSAFWIFETVSQS KQSLTSLVYS  
 VNELLVLSNLAQWALG (SEQ ID NO:427), AWKPKGTDDICTSHNTTHIQKMP  
 (SEQ ID NO:428), CPRGAKSYHIDCWPPALFPRCVAYL (SEQ ID NO:429), SYHI  
 DCWPPALFPRCVAYLFLNKPAT (SEQ ID NO:430), and/or RKKYYCKPY  
 HTQLHPAWHREKSAFWIFET (SEQ ID NO:431). Polynucleotides encoding these  
 15 polypeptides are also encompassed by the invention.

This gene is expressed primarily in dendritic cells and activated monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
 20 not limited to, immune or hematopoietic disorders, particularly inflammation, immune defects, multiple myeloma, or immunodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at  
 25 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 30 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:237 as residues: Thr-27 to Arg-33.

The tissue distribution in dendritic cells and monocytes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the  
 35 diagnosis and treatment of inflammatory and immune disorders such as cancers, particularly of dendritic cells and monocytes, but also of hematopoietic progenitors. Similarly, polynucleotides and polypeptides corresponding to this gene are useful for

the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency, etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:112 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1538 of SEQ ID NO:112, b is an integer of 15 to 1552, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 103

When tested against K562 leukemia cell lines, supernatants removed from cells containing this gene activated the ISRE assay. Thus, it is likely that this gene activates leukemia cells through the Jak-STAT signal transduction pathway. The interferon-sensitive response element is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The gene encoding the disclosed cDNA is thought to reside on chromosome 5.

Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in placenta, adipose tissue and fibroblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the skin, developing organs and metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermal system metabolic system and embryogenesis, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. epidermal, cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of disorders of the epidermal system, metabolic system and embryogenesis. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:113 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:113, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.

5

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 104

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ICLDSCSQVSVTSLWSFLRVHSLVQTLW (SEQ ID NO:432). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including neutropenia, cancer, inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:239 as residues: Ala-35 to Asp-44.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases of the immune system since expression is primarily in neutrophils, and may be useful as a growth factor for the differentiation or proliferation of neutrophils for the treatment of neutropenia following chemotherapy or may be useful in the treatment of immune dysfunction or anti-inflammatory by inhibiting infiltration of neutrophils to the site of injury or distress. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:114 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 593 of SEQ ID NO:114, b is an integer of 15 to 607, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 105

This gene is expressed primarily in stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in stromal cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune disorders. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease,

sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:115 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1484 of SEQ ID NO:115, b is an integer of 15 to 1498, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 106

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HYCC DFGTSL LGFYVPFHYYVH MVNIIL TTIDFYHYKFC CSQNANKHCFKHFQIMTTVPYLNINKENLRFKNIF K (SEQ ID NO:433), TSL LGFYVPFHYYVH MVNIIL TTIDFY (SEQ ID NO:434), and/or FQIMTTVPYLN INKENLRFKNI (SEQ ID NO:435). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in spleen, breast, placenta, ovarian cancer, and to a lesser extent, in B-cell lymphoma, pancreas tumor, osteoclastoma, thyroid, bone marrow, fetal liver, and stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases characterized by immune cell activation and proliferation, particularly of the reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
5 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, reproductive, metabolic, skeletal, endocrine, hepatic, placental, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile,  
10 amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
15 NO:241 as residues: Ser-21 to Ser-27.

The tissue distribution in spleen and reproductive tissues indicates that the product of this gene is useful for modifying or detecting the proliferation or activation of cells in the hematopoietic system. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or  
20 receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy);  
25 regulation of hematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-  
30 inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behaviour. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the  
35 above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:116 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more

- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1783 of SEQ ID NO:116, b is an integer of 15 to 1797, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.

10

## **FEATURES OF PROTEIN ENCODED BY GENE NO: 107**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

- 15 ISESMSLVRS LQFYRGKNRAERTVISSSSHSCHLIDLEFQPRSDGEVSISFLEKGV  
ELRWGMGLEDLIGLGLGVSTRRSTVRRKEPTKAGMHTACSEEMEPENREN  
(SEQ ID NO:436), DGSRSVAQARVQWHHRGSLPPLPPRFKQFPLRHLRVGGITG  
ACRHTQIIFVVLVQMGFHHVG QAGLELLTSGDPPALASQSAGITGVSHSTRPKL  
LSWLPSDNLLGMALYSIQWALLANS LYFQVPSPLSML CAFLPLWVPSA (SEQ  
20 ID NO:437), RGKNRAERTVISSSSHSCHLIDLEFQ (SEQ ID NO:438), LGLGVST  
RRSTVRRKEPTKAGMHTACSEEMEP (SEQ ID NO:439), GDPPALASQSAGI  
TGVSHSTRPKL (SEQ ID NO:440), and/or ALYSIQWALLANS LYFQVPSPLSML  
(SEQ ID NO:441). Polynucleotides encoding these polypeptides are also encompassed  
by the invention.

- 25 This gene is expressed primarily in bone marrow.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly bone marrow related  
30 diseases such as multiple myeloma, immunodeficiencies, and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone marrow, expression of this gene at significantly higher or lower levels may be routinely  
35 detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:242 as residues: Gln-46 to Asn-56.

5           The tissue distribution in bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of central nervous system disorders and hemopoietic system developmental disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia,  
10   pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection,  
15   inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:117 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

25   Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 938 of SEQ ID NO:117, b is an integer of 15 to 952, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.

30

## **FEATURES OF PROTEIN ENCODED BY GENE NO: 108**

35           In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DRILLFYSRDQGTTSTKGPNPACCLFLLKKFYWNTA (SEQ ID NO:442), and/or DGQTTSTKGPNPACCLFLLKKF (SEQ ID NO:443).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in early stage human brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly developmental disorders of the brain. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the early stage human brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:243 as residues: Asn-16 to Gln-21.

The tissue distribution in early stage brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of brain development disorders. In addition, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Moreover, the expression within embryonic tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly,

developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:118 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1171 of SEQ ID NO:118, b is an integer of 15 to 1185, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 109

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DPRVRRITLDLGITLYLFLYIFLSL (SEQ ID NO:444), PALGECCLDAFLFLLGKQLKKSGEKPLLGGSLMEYAILS AIAAMNEPKTCSTTA LKKYV LENHPGTNSNYQMHL LKKTLQKCEKNGWMEQISGKGFSGTFQL CFPYYPSPGVLFPPKKEPDDSRDEDEDE DESSEEDSEDEEPPPKRRLQKKTPAKS PGKAASVKQRGSKPAPKVSA AQRGKARPLPKKAPPAKTPAKK TRPSSTV IKKPSGGSSKKPAT SARKEVKLPKGKSTMKKSFRVKK (SEQ ID NO:445), DFEFHHDTLFSYKIYFFTLKDFFMVDLPLPGNFTSFLALVAGFF EEPPLGFLM TVDEGLVFLAGVLALGGAFLGKGLAFPRWAAETLGAGLDPLCFTDAAFPGDLA GVFFCNLL LGGGSSSSSESSSDSSSSSSSSLESSGSFFGNRTPGLG (SEQ ID NO:446), CLDAFLFLLGKQLKKSGEKPLLGGSLME (SEQ ID NO:447), YQMHL LKKTLQKCEKNGWMEQISGKGFSGT (SEQ ID NO:448), KTPAKSPGKAAS VKQRGSKPAPKVSA AQRGKARPLPKKAPPAKTPAKK TRPSSTV IKKPSGGSSKKPAT SARKEVKLPKGKSTMKKSFR (SEQ ID NO:450), VDEGLVFLAGVLALGGAFLGKGL (SEQ ID NO:451), and/or GLDPLCFTDAAFPGDLAGVFFCNLL (SEQ ID NO:452). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in bone marrow stromal cells, and to a lesser extent, in human osteoblasts and T cells (helper I).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, connective tissues, haemopoietic, or immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. hematopoietic, immune, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:244 as residues: Glu-18 to Cys-38.

The tissue distribution in bone marrow stromal cells and T-cells suggest that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of defects of stromal development, and immune system disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the expression of this gene product in osteoblasts would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal

chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:119 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1084 of SEQ ID NO:119, b is an integer of 15 to 1098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 110**

This gene is expressed primarily in rhabdomyosarcoma, CD34 positive cells, breast lymph nodes, neutrophils and endothelial cells.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, developmental, proliferative, and vascular disorders, particularly fibroids or atherosclerosis. Similarly, polypeptides and  
25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune or hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, hematopoietic, developmental, vascular,  
30 endothelial, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 The tissue distribution in neutrophils and lymph nodes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of disorders in immune or hematopoietic systems. Similarly,

the secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behaviour. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. The protein may also show utility in the treatment or prevention of a variety of vascular disorders, particularly embolism, thrombosis, aneurysms, stroke, or atherosclerosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:120 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 791 of SEQ ID NO:120, b is an integer of 15 to 805, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 111

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: TMLFYLSQPDWQLDFFRVSFNG PVFFIIIFNDRAGFRM QALVSQAACRRSRYKLSVVY (SEQ ID NO:453), and/or DRAGFRMQALVS

QAACRRSRYKL (SEQ ID NO:454). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

5           This gene is expressed primarily in human cerebellum, and to a lesser extent, in colon carcinoma cells, activated T-cells, fetal spleen, and placenta.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, or neural disorders, particularly  
10           neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune or central nervous systems, expression of this gene at  
15           significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
20           fluid from an individual not having the disorder.

          The tissue distribution in human cerebellum indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of diseases in the central nervous system and immune disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the  
25           detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania,  
30           dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation,  
35           neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo,

sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:121 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1584 of SEQ ID NO:121, b is an integer of 15 to 1598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 112**

The gene encoding the disclosed cDNA is thought to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in testes, fetal brain, and fetal liver.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain and liver diseases, reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and brain expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, reproductive, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and liver tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of neural, hepatic, or metabolic diseases. Furthermore, the tissue distribution indicates that

polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the brain and nervous system. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; 5 or Alzheimer's. The tissue distribution further indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Additionally, the tissue distribution indicates that the protein product 10 of this gene is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, 15 the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and 20 kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ 25 ID NO:122 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of 30 a-b, where a is any integer between 1 to 1006 of SEQ ID NO:122, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.

### 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 113

This gene is expressed primarily in apoptotic T-cells, and to a lesser extent, in the frontal cortex of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. Immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:248 as residues: Arg-19 to Gly-36, Val-44 to Leu-59.

The tissue distribution in apoptotic T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of immune disorders. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation,

neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:123 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1364 of SEQ ID NO:123, b is an integer of 15 to 1378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 114**

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly inflammatory conditions or immunodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification  
25 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. immune, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual  
30 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a  
35 malfunctioning immune system response to foreign antigens. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by

boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Expression of this gene product in neutrophils also strongly indicates a role for this  
 5 protein in immune function and immune surveillance.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:124 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
 10 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1132 of SEQ ID NO:124, b is an integer of 15 to 1146, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.  
 15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 115

20 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LAAGILNSSLPALYHSVEEISQ (SEQ ID NO:455), XYRMNT KFLESYKMSTTLRRHQNVSLCKDMKTPAGTDTKIAFLE (SEQ ID NO:456), SYKMSTTLRRHQNVSLCKDM (SEQ ID NO:457), ICIESLMLHYIALVFEMAF MFPLVYHEMGSDSIRFHLQCVDSCLPMMRFFFSFPFL (SEQ ID NO:458), YI  
 25 ALVFEMAFMFPLVYHEMG (SEQ ID NO:459), and/or SDSIRFHLQC VDSCLPMMRF (SEQ ID NO:460). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in melanocytes, merkel cells, synovial cells, ulcerative colitis, and to a lesser extent, in fetal spleen, bone marrow, jurkat cells,  
 30 adrenal gland tumor rejected kidney from a failed transplantation.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, integumentary, skeletal, or gastrointestinal disorders, particularly  
 35 tumors, including melanoma, lymphoma, and adrenal gland tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a

number of disorders of the above tissues or cells, particularly of the integumentary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Integumentary, skeletal, gastrointestinal, immune, hematopoietic, renal, endocrine, and cancerous and wounded tissues) or  
5 bodily fluids (e.g. lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in melanocytes indicates that polynucleotides and  
10 polypeptides corresponding to this gene are useful for detecting and treating tumors particularly those involving melanocytes, lymphocytes and the adrenal gland. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of  
15 biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anaemia or as adjunct to chemotherapy); stimulation  
20 or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as  
25 antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behaviour. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:125 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.  
35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1661 of SEQ ID NO:125, b is an integer of 15

to 1675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 116

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates fibroblast cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

15 GGVSVDGSLREETDVGEGGRPRGGQSEGARVTRRPSPDSDNASAFDLDLDFS  
PFCIWVYRLETAEVVF SPAPLRLSGPGLAPVVFVSTLPSLQSSFCGWD  
LPARPRGLSGFR (SEQ ID NO:461), FTKSCSKMSSTHLYKGSVDLCYARS  
SESMSLSCGDVANAGR LTPRLHLARSASQGPPTLPRVPPRGSRPPTA GESPA  
PRTXSLENHKNIDHLSSNSHGKFRIYGQNDIKI (SEQ ID NO:462), QDVIYTFVQ  
20 RFRPMLCTILRKYEPVVRGRRKRWQA HPSSAFGKKRLPRPPHPAQGAPQRE  
QASHSWREPGPQNTFFPRKP (SEQ ID NO:463), REETDVGEGGRPRGGQSEGA  
RV (SEQ ID NO:464), GPGLAPVVFVSTLPSLQSSFCGWDLP (SEQ ID NO:465),  
MSSTHLYKGSVDLCYARSSSESMSL (SEQ ID NO:466), SQGPPTLPRVPPRG  
SRPPTAGESPAPRT (SEQ ID NO:467), RFRPMLCTILRKYEPVVRGRRKRW  
25 (SEQ ID NO:468), and/or RLPRPPHPAQGAPQREQASHSWRE (SEQ ID NO:469).  
Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in hematopoietic cells, endothelial cells, and in spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as  
30 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, hematopoietic, integumentary, and immune disorders, particularly  
multiple myeloma, immunodeficiencies, leukemias, and vascular conditions. Similarly,  
polypeptides and antibodies directed to these polypeptides are useful in providing  
35 immunological probes for differential identification of the tissue(s) or cell type(s). For a  
number of disorders of the above tissues or cells, particularly of the hematopoietic,  
immune, and vascular systems, expression of this gene at significantly higher or lower

levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, integumentary, endothelial, and cancerous and wounded tissues) or bodily fluids (e.g.lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to  
5 the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen and hematopoietic cells, combined with the detected EGR1 biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of vascular,  
10 immune and/or hematopoietic disorders including arthritis, ischemia, auto-immune diseases, host-graft rejection, AIDS, leukemia and microbial infection. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the  
15 production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the  
20 expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, a utility for treating or preventing vascular or integumentary disorders may be anticipated for this gene based upon its expression within endothelial tissues in addition to its EGR1 activity. Protein, as well as, antibodies directed against the protein may show utility as a  
25 tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:126 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
30 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1050 of SEQ ID NO:126, b is an integer of 15 to 1064, where both a and b correspond to the positions of nucleotide residues shown  
35 in SEQ ID NO:126, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 117

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

5 RGMGRWLVS SGA AFPIPLNGFCESREFFPD SGSVLLHWRPNXVLIEIKVFGS  
 RSQSLISSK NLKTS LTFIYGKVEEV LNN (SEQ ID NO:470), LKLSSADSQA  
 IMNIFSADCM PRLHIALQTEMIPN RAPQGGAAANLWHEAQYRRLPFSR APEX  
 TDAHQASAQRGAAQLPREQ (SEQ ID NO:471, PIPLNGFCESREFFPD SG  
 10 VLLHWRPNX (SEQ ID NO:472), and/or NIFSADCM PRLHIALQTEMIP NRA  
 PQGGA (SEQ ID NO:473). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as

15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the immune system, including neutropenia, cancer, inflammatory diseases and allergies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

20 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another

25 tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment/diagnosis of diseases

30 of the immune system since expression is primarily in neutrophils, and may be useful as a growth factor for the differentiation or proliferation of neutrophils for the treatment of neutropenia following chemotherapy or may be useful in the treatment of immune dysfunction or anti-inflammatory by inhibiting infiltration of neutrophils to the site of injury or distress. Protein, as well as, antibodies directed against the protein may show

35 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:127 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more

- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1593 of SEQ ID NO:127, b is an integer of 15 to 1607, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 118**

- Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of renal mesangial cells to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both mesangial cells and other cell types, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating mesangial cells. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell. In addition, when tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates fibroblast cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:
- 15  
20  
25  
30

TFRLVSAHLKTRKLINPEAAERRWRDWDSRQGWLSVK (SEQ ID NO:474), and/or KTRKLINPEAAERRWRDWDSR (SEQ ID NO:475). Polynucleotides encoding these polypeptides are also encompassed by the invention.

- This gene is expressed primarily in bone marrow cell lines, and to a lesser extent, in human endometrial stromal cells, human adult small intestine and human pancreas tumor.
- 35

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic and gastrointestinal tract disorders and stromatosis, in addition to endothelial, mucosal, or epithelial cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and digestive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. hemaopoietic, immune, reproductive, gastrointestinal, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:253 as residues: Gly-25 to Arg-31, Ile-47 to Glu-57, Glu-120 to Arg-138.

The tissue distribution in bone marrow cells, combined with the detected calcium flux and EGR1 biological activity indicates that polynucleotides and polypeptides corresponding to this gene are useful for immune and gastrointestinal tract disorders, and stromatosis, particularly tumors and proliferative disorders. More specifically, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:128 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:128, b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 119

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: WNYTVNNLYLFSFSIVSMKFMHVLSINIF FGRARWLT PVIPALLEAEAGGSLGQEFKTSLGKDGETPSLLKIQKLAGHGGRRRL (SEQ ID NO:476, DQPGKHGETLSLLKMQLTWCGGMPFVIP SYSRSPRPENRLNL GDRGCTELLHSSLGNRVRLSKKKEVYMMELYSK (SEQ ID NO:477), VIPALLE AEAGGSLGQEFKTSLGKDGET (SEQ ID NO:478), and/or NRLNLGDRGCT ELLHSSLGNRVRLSKKKE (SEQ ID NO:479). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, developmental, and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. neural, developmental, immune, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders relating to CNS and immune system. In addition, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of

neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Furthermore, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:129 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1132 of SEQ ID NO:129, b is an integer of 15 to 1146, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 120

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASEHLAALPVNVKIGK (SEQ ID NO:480). Polynucleotides

encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

5 This gene is expressed primarily in T cells/helper I.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, or haemopoietic disorders. Similarly, polypeptides and  
10 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Immune, haemopoietic disorders, and cancerous and wounded tissues)  
15 or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
20 NO:255 as residues: Ile-31 to Glu-36, Leu-59 to Glu-73, Ser-109 to Ser-121, Ser-175 to Gln-182, Lys-258 to Lys-264.

The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders. Moreover, expression of this gene product indicates a role in regulating the  
25 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved  
30 in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as  
35 host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease,

scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:130 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1158 of SEQ ID NO:130, b is an integer of 15 to 1172, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 121

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:  
LVCILLVHWIPPLGAWGLSLMLFLILEQRCGKGKWRNALLSVSFSVPQLQMOK  
VS LDSTPLNVNHDKMDIWKLTPKL (SEQ ID NO:481), IMIKWIFGNLLL SCD  
LGCISTSGLPQYQGLRLLNFEYSLGFMLRSLWSRSAIQCFES (SEQ ID NO:482),  
LLLSCDLGCISTSGLPQYQGL (SEQ ID NO:483), and/or LRLNFEYSLGFM  
LRSLWSRS (SEQ ID NO:484). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in human gall bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic, or gastrointestinal disorders, particularly those relating to the gall bladder. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of

the gastrointestinal tract system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. Metabolic, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:256 as residues: Ser-18 to Gly-26.

The tissue distribution in gall bladder tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of gall bladder disorders, or related metabolic conditions, such as gall stones. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:131 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 649 of SEQ ID NO:131, b is an integer of 15 to 663, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 122

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ASPHL FIEKWGRAFILRKLLLVPVISKRIINIMAHQVKPPI FCAMIMCNLFCSGYEHL LFTLMRFFSFEQIFDEV VFH (SEQ ID NO:485), and/or KLLLVPVISKRIINIMAH QVK PPIF (SEQ ID NO:486). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in glioblastoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly glioblastoma multiform. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system (CNS), expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. neural, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:257 as residues: Ser-40 to Gly-45, Leu-73 to Arg-80.

The tissue distribution in glioblastoma indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of neural cell disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:132 and may have been publicly available prior to conception of the present

invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 762 of SEQ ID NO:132, b is an integer of 15 to 776, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 123

When tested against U937 and Jurket cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, including their progenitors, through the Jak-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

FAVIRFESIIHEFDPWFNYRSTHHLASHGFIYEFNLNWFDERAWYPLGRIVGGTVY  
 PGLMITAGLIHWILNT LNITVHIRDVCVFLAPTFSGLTSISTFLLTRELWN QGA  
 GLLAACFIAIVPGYISRSVAGSFDNEGIAIFA LQFTYYLWVKS VKTGSVFW  
 25 TMCCCLSYFYMVSAWGGYVFIIINLIPLHVFVLLLMQRYSKRVYIAYSTFYI VGL  
 ILSMQIPFVGFGPIRTSEHMAAAGVFALLQAY AFLQYLRDRLTKQEFQTLFFLG  
 SLAAGAVFLSVI YLTYTG YIAPW SGRFYS LWDTGYAKIHIPIASVSEHQ PTT  
 WVSFFFDLHILVCTFPAGLWFCIKNINDE RXFGKXGF (SEQ ID NO:487), EFD  
 PWFNYRSTHHLASHGFIYEFNLNWF (SEQ ID NO:488), TRELWNQGAGLL  
 30 AACFIAIVPGY (SEQ ID NO:489), TYYLWVKS VKTGSVFWTMCCCL (SEQ ID  
 NO:490), GV FALLQAY AFLQYLRDRLTKQEFQ (SEQ ID NO:491), and/or YSLWD  
 TGYAKIHIPIASVSEHQPTTW (SEQ ID NO:492). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human colon carcinoma (HCC) cell line, and to a lesser extent, in human eosinophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal or immune disorders, particularly colon carcinoma and leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the excretory and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. gastrointestinal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:258 as residues: Glu-49 to Ser-54.

The tissue distribution in human colon carcinoma cell lines, combined with the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of colon cancer and immune disorders. In addition, expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy, particularly in modulating the immune response to cancer-specific antigens. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:133 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1529 of SEQ ID NO:133, b is an integer of 15 to 1543, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 124

- 5           This gene shares homology with elongation factor 1-Alpha (*giardia intestinalis*), which promotes the GTP-dependent binding of aminoacyl tRNA to the A-site of ribosomes during protein biosynthesis. One embodiment of this gene comprises polypeptides of the following amino acid sequence:
- MGHMLYLLGNINKRTMHKYXQESKKAGKASFAY AWWLDETGEERER
- 10   GVTMDVGMTKFETTTKVIT LMDAPGHKDFIPNMITGAAQADVAVLVVDASR  
 GEFEAGFETGGQTREHGLLVRS LGVTQLAVAVN KMDQVNWQQERF QEIT  
 GKLGHFLKQAGFKESDV GFIPTSGLSGENLITRSQSSELTKWYKGLCLLEQ  
 IDSFKPPQRSIDKPFRLCVSDVFKDQSGGFCITG KIEAGYIQTGDRLL AMP  
 NETCTVKGITLHDEPV DWAAAGDHVSLTLVGMDIIKINVGCFGPKVP
- 15   IKACTRFRARILIFNIEIPITKGFPVLLHYQTVSE PAVIKRLISVLNKSTG  
 EVTKKKPKFLTKGQNAL VELQTQRPIALELYKDFKELGRFMLRYGGSTIAA  
 GVVTEIKE (SEQ ID NO:493), LYLLGNINKRTMHKYXQESKK (SEQ ID  
 NO:494), LDETGEERERGV TMDVGMTKFET (SEQ ID NO:495), GHKDFIPNMIT  
 GAAQADVAVLV (SEQ ID NO:496), GFETGGQTREHGLLVRS LGVTQL (SEQ ID  
 20   NO:497), WQERFQEITGKLGHFLKQAGFK (SEQ ID NO:498), TSGLSGENLI  
 TRSQSSELTKWY (SEQ ID NO:499), PQRSIDKPFRLCVSDVFKDQSG (SEQ ID  
 NO:500), LISVLNKSTGEVTKKKPKFLTK (SEQ ID NO:501), and/or QRPIALELY  
 KDFKELGRFMLRYGGS (SEQ ID NO:502). An additional embodiment is the  
 polynucleotides encoding these polypeptides. The gene encoding the disclosed cDNA is  
 25   thought to reside on chromosome 6. Accordingly, polynucleotides related to this  
 invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in colon tissue from a patient having ulcerative colitis, brain tissue, lung tissue, testes and endometrial tumor.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 30   reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ulcerative colitis, and testes and endometrial tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a
- 35   number of disorders of the above tissues or cells, particularly of the immune system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, immune,

cancerous and wounded tissues) or bodily fluids (e.g., serum, seminal fluid, pulmonary surfactant or sputum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in ulcerative colitis, testes and endometrial tumors indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing or treatment of a variety of reproductive or gastrointestinal disorders. Furthermore, the tissue distribution indicates that the protein product of this gene is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:134 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2143 of SEQ ID NO:134, b is an integer of 15 to 2157, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 125**

This gene is expressed primarily in skin.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, integumentary diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
5 tissues or cells, particularly of the integumentary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues and cell types (e.g. integumentary, melanocyte, and cancerous and wounded tissues) or bodily fluids (e.g. lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the  
10 standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in skin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of diseases relating to integumentary conditions. Specifically, polynucleotides and polypeptides  
15 corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and  
20 inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to  
25 viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as  
30 rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets  
35 for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:135 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more
- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 406 of SEQ ID NO:135, b is an integer of 15 to 420, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HUSIG64	209423 10/30/97	pSport1	11	1010	1	1010	9	9	136	1	21	22	334
2	HATCI78	209368 10/16/97	Uni-ZAP XR	12	1559	1	1559	283	283	137	1	20	21	42
3	HSIDR70	209368 10/16/97	Uni-ZAP XR	13	1589	1	1589	110	110	138	1	17	18	86
4	HFADD53	209368 10/16/97	Uni-ZAP XR	14	1255	1	1255	183	183	139	1	22	23	121
5	HPMGT51	209423 10/30/97	Uni-ZAP XR	15	1191	1	1191	152	152	140	1	29	30	275
6	HFVAB79	209368 10/16/97	Uni-ZAP XR	16	1186	1	1186	139	139	141	1	15	16	194
7	HDTBP51	209407 10/23/97	pCMVSPORT 2.0	17	1182	1	1182	93	93	142	1	25	26	182

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
8	HLHFR19	209407 10/23/97	Uni-ZAP XR	18	1171	1	1171	24	24	143	1	30	31	121
9	HMEET96	209407 10/23/97	Lambda ZAP II	19	1337	73	1200	121	121	144	1	30	31	266
10	HTXCV12	209423 10/30/97	Uni-ZAP XR	20	1162	1	1162	183	183	145	1	27	28	91
11	HCEFB70	209423 10/30/97	Uni-ZAP XR	21	1837	1	1837	223	223	146	1	24	25	108
12	HDTAV25	209423 10/30/97	pCMVSPORT 2.0	22	1054	1	1054	100	100	147	1	38	39	87
13	HSATA21	209368 10/16/97	Uni-ZAP XR	23	1066	1	1060	49	49	148	1	25	26	73
14	HKIXI03	209368 10/16/97	pBluescript	24	928	1	928	61	61	149	1	24	25	71
15	HDTDC56	209407 10/23/97	pCMVSPORT 2.0	25	966	1	966	210	210	150	1	24	25	151

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
16	HLTBF35	209407 10/23/97	Uni-ZAP XR	26	1146	1	1132	136	136	151	1	16	17	60
17	HEPAB80	209423 10/30/97	Uni-ZAP XR	27	802	1	802	67	67	152	1	28	29	122
18	HFOXBI3	209423 10/30/97	pSport1	28	1169	1	1169	36	36	153	1	21	22	54
19	HTOAK16	209368 10/16/97	Uni-ZAP XR	29	1466	1	1466	87	87	154	1	18	19	110
20	HBXDC63	209368 10/16/97	ZAP Express	30	1226	1	1226	165	165	155	1	30	31	47
21	HASAU43	209407 10/23/97	Uni-ZAP XR	31	1094	1	1094	33	33	156	1	17	18	81
22	HAGEA31	209423 10/30/97	Uni-ZAP XR	32	1037	1	1037	151	151	157	1	25	26	155
23	HEQAF19	209423 10/30/97	pCMVSPORT 3.0	33	1376	1	1376	84	84	158	1	23	24	294

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO:	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO:	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
24	HTXHB33	209368 10/16/97	Uni-ZAP XR	34	1220	1	1220	243	243	159	1	17	18	59
25	HMWFT65	209368 10/16/97	Uni-Zap XR	35	1346	1	1346	72	72	160	1	28	29	121
26	HNGAZ68	209368 10/16/97	Uni-ZAP XR	36	1026	1	1026	238	238	161	1	18	19	72
27	HTWFH07	209407 10/23/97	pSport1	37	832	1	832	14	14	162	1	25	26	122
28	HMQDF12	209407 10/23/97	Uni-ZAP XR	38	706	1	627	63	63	163	1	27	28	142
29	HFABH95	209407 10/23/97	Uni-ZAP XR	39	1347	1	1347	199	199	164	1	21	22	116
30	HNGDD48	209423 10/30/97	Uni-ZAP XR	40	1467	1	1467	85	85	165	1	20	21	58
31	HPMBY46	209423 10/30/97	Uni-ZAP XR	41	914	1	914	63	63	166	1	21	22	125

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HRKPA09	209423 10/30/97	pBluescript	42	1131	1	1131	101	101	167	1	33	34	86
33	HAGAQ26	209368 10/16/97	Uni-ZAP XR	43	1333	157	1333	251	251	168	1	20	21	62
34	HCWFL55	209368 10/16/97	ZAP Express	44	1004	1	1004	40	40	169	1	19	20	47
35	HKAAB44	209368 10/16/97	pCMVSPORT 2.0	45	1494	1	1494	113	113	170	1	39	40	136
36	HNGEU90	209407 10/23/97	Uni-ZAP XR	46	1166	1	1166	17	17	171	1	20	21	88
37	HCFC07	209407 10/23/97	pSport1	47	1536	1	1536	94	94	172	1	47	48	57
38	HLWBI63	209407 10/23/97	pCMVSPORT 3.0	48	1038	1	1038	149	149	173	1	30	31	63
39	HIDUAC77	209423 10/30/97	pSport1	49	1176	1	1176	193	193	174	1	19	20	60

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
40	HFOYV27	209423 10/30/97	pSport1	50	731	1	731	171	171	175	1	18	19	103
41	HGBHI35	209423 10/30/97	Uni-ZAP XR	51	1437	71	1276	87	87	176	1	16	17	292
42	HRDEU27	209423 10/30/97	Uni-ZAP XR	52	1369	1	1369	285	285	177	1	18	19	45
43	HNGJE50	209368 10/16/97	Uni-ZAP XR	53	1037	1	1037	77	77	178	1	36	37	46
44	HNHJU48	209368 10/16/97	Uni-ZAP XR	54	1373	1	1373	99	99	179	1	20	21	54
45	HFXJU68	209423 10/30/97	Lambda ZAP II	55	1347	1	1347	148	148	180	1	25	26	66
46	HMMAH60	209368 10/16/97	pSport1	56	822	1	822	142	142	181	1	15	16	50
47	HNGFR31	209407 10/23/97	Uni-ZAP XR	57	536	1	536	108	108	182	1	23	24	90

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
48	HFPDB26	209423 10/30/97	Uni-ZAP XR	58	1262	50	1192	65	65	183	1	29	30	54
49	HFRAW86	209423 10/30/97	Uni-ZAP XR	59	1269	1	1269	162	162	184	1	16	17	63
50	HTEDX90	209368 10/16/97	Uni-ZAP XR	60	1829	1	1829	63	63	185	1	17	18	112
51	HTXGG45	209407 10/23/97	Uni-ZAP XR	61	1112	1	1112	52	52	186	1	19	20	59
52	HTXJI95	209407 10/23/97	Uni-ZAP XR	62	1674	1	1674	164	164	187	1	23	24	63
53	HLYBD32	209407 10/23/97	pSport1	63	1045	35	1045	98	98	188	1	23	24	70
54	HOUDK26	209423 10/30/97	Uni-ZAP XR	64	1051	1	1051	218	218	189	1	24	25	62
55	HROAJ03	209423 10/30/97	Uni-ZAP XR	65	1182	1	1182	19	19	190	1	20	21	192

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
56	HTXAJ12	209423 10/30/97	Uni-ZAP XR	66	675	1	675	91	91	191	1	18	19	111
57	HKAEL80	209423 10/30/97	pCMVSPORT 2.0	67	1105	1	1105	398	398	192	1	17	18	79
58	HNHFL04	209423 10/30/97	Uni-ZAP XR	68	1279	1	1279	162	162	193	1	16	17	87
59	HPCAM01	209368 10/16/97	Uni-ZAP XR	69	1638	1	1638	311	311	194	1	24	25	41
60	HJACA79	209368 10/16/97	pBluescript SK-	70	887	1	887	84	84	195	1	28	29	68
61	HMADK33	209368 10/16/97	Uni-ZAP XR	71	864	1	864	161	161	196	1	24	25	152
62	HMSFI26	209368 10/16/97	Uni-ZAP XR	72	1217	1	1217	120	120	197	1	34	35	62
63	HMSJR08	209368 10/16/97	Uni-ZAP XR	73	1717	1	1717	165	165	198	1	28	29	63

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
64	HMWIO93	209368 10/16/97	Uni-Zap XR	74	1276	1	1276	72	72	199	1	18	19	42
65	HNGAK47	209368 10/16/97	Uni-ZAP XR	75	1144	1	1144	89	89	200	1	23	24	40
66	HNGAL31	209368 10/16/97	Uni-ZAP XR	76	918	1	918	34	34	201	1	20	21	43
67	HNGIZ06	209368 10/16/97	Uni-ZAP XR	77	1065	1	1065	108	108	202	1	16	17	41
68	HNHBI75	209368 10/16/97	Uni-ZAP XR	78	1126	1	1126	12	12	203	1	15	16	41
69	HOFNT24	209368 10/16/97	pCMVSPORT 2.0	79	984	1	984	63	63	204	1	22	23	112
70	HSAXI95	209368 10/16/97	Uni-ZAP XR	80	1247	1	1247	147	147	205	1	19	20	44
71	HCMTB45	209368 10/16/97	Uni-ZAP XR	81	946	1	946	209	209	206	1	27	28	70

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
72	HE9CP41	209368 10/16/97	Uni-ZAP XR	82	1392	1	1392	132	132	207	1	21	22	41
73	HHENV10	209368 10/16/97	pCMVSPORT 3.0	83	1155	1	1155	143	143	208	1	27	28	50
74	HSKDD72	209407 10/23/97	Uni-ZAP XR	84	1373	1	1373	94	94	209	1	23	24	64
75	HAGDO20	209407 10/23/97	Uni-ZAP XR	85	1258	184	1258	218	218	210	1	20	21	76
76	HCFBH15	209407 10/23/97	pSPORT1	86	1318	1	1318	156	156	211	1	22	23	44
77	HSYBX48	209423 10/30/97	pCMVSPORT 3.0	87	978	38	961	246	246	212	1	34	35	65
78	HATDQ62	209423 10/30/97	Uni-ZAP XR	88	1863	323	1863	412	412	213	1	25	26	61
79	HMEJE13	209423 10/30/97	Lambda ZAP II	89	2086	1	1131	147	147	214	1	26	27	55

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
80	HNAAF65	209423 10/30/97	pSport1	90	891	1	891	140	140	215	1	21	22	212
81	HNHFY30	209423 10/30/97	Uni-ZAP XR	91	1974	1	1974	134	134	216	1	30	31	40
82	HNFI81	209423 10/30/97	pBluescript	92	1423	1	1423	19	19	217	1	20	21	59
83	HNTBI57	209423 10/30/97	pCMVSPORT 3.0	93	1365	134	1365	210	210	218	1	26	27	58
84	HSAYR13	209423 10/30/97	Uni-ZAP XR	94	756	1	756	171	171	219	1	19	20	45
85	HTOHV49	209407 10/23/97	Uni-ZAP XR	95	938	1	729	62	62	220	1	19	20	61
86	HSFAG37	209368 10/16/97	Uni-ZAP XR	96	928	1	928	264	264	221	1	18	19	51
87	HTXBU52	209407 10/23/97	Uni-ZAP XR	97	1715	557	1715	574	574	222	1	34	35	50

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
88	HLHFP18	209407 10/23/97	Uni-ZAP XR	98	678	1	678	25	25	223	1	24	25	46
89	HFXBW09	209423 10/30/97	Lambda ZAP II	99	1541	1	1541	159	159	224	1	29	30	51
90	HNGEM62	209423 10/30/97	Uni-ZAP XR	100	881	1	881	78	78	225	1	21	22	65
91	HNGJF92	209423 10/30/97	Uni-ZAP XR	101	947	1	947	40	40	226	1	31	32	46
92	HMEED18	209368 10/16/97	Lambda ZAP II	102	1369	28	1369	34	34	227	1	34	35	221
93	HMIAM45	209368 10/16/97	Uni-ZAP XR	103	1231	1	1231	68	68	228	1	37	38	48
94	HSAVK10	209368 10/16/97	Uni-ZAP XR	104	1242	1	1242	131	131	229	1	32	33	40
95	HSDHC81	209368 10/16/97	Uni-ZAP XR	105	1151	1	1151	184	184	230	1	22	23	52

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
96	HSLCT04	209368 10/16/97	Uni-ZAP XR	106	1628	1	1628	159	159	231	1	36	37	49
97	HMDAB56	209368 10/16/97	Uni-ZAP XR	107	1465	1	1465	273	273	232	1	33	34	44
98	HUDBZ89	209407 10/23/97	ZAP Express	108	1265	1	1265	197	197	233	1	17	18	54
99	HL YCT47	209407 10/23/97	pSport1	109	1006	1	1006	47	47	234	1	22	23	68
100	HOSDJ25	209423 10/30/97	Uni-ZAP XR	110	1258	1	1258	146	146	235	1	18	19	40
101	HADAO89	209423 10/30/97	pSport1	111	1453	1	1453	244	244	236	1	22	23	44
102	HMSG14	209423 10/30/97	Uni-ZAP XR	112	1552	1	1552	138	138	237	1	18	19	77
103	HPMGD01	209423 10/30/97	Uni-ZAP XR	113	1489	140	1489	157	157	238	1	36	37	52

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
104	HNHFU32	209407 10/23/97	Uni-ZAP XR	114	607	1	607	175	175	239	1	30	31	52
105	HMIAL40	209368 10/16/97	Uni-ZAP XR	115	1498	1	1498	235	235	240	1	19	20	42
106	HAMFY69	209407 10/23/97	pCMVSPORT 3.0	116	1797	314	1797	359	359	241	1	17	18	48
107	HBMCT17	209407 10/23/97	pBluescript	117	952	1	952	160	160	242	1	25	26	74
108	HEBF191	209407 10/23/97	Uni-ZAP XR	118	1185	1	1185	132	132	243	1	20	21	43
109	HHEAH86	209407 10/23/97	pCMVSPORT 3.0	119	1098	1	1098	75	75	244	1	16	17	64
110	HRDFD27	209423 10/30/97	Uni-ZAP XR	120	805	1	805	82	82	245	1	36	37	83
111	HTPCS72	209423 10/30/97	Uni-ZAP XR	121	1598	306	1598	530	530	246	1	29	30	71

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
112	HFFAL36	209368 10/16/97	Lambda ZAP II	122	1020	1	1020	68	68	247	1	35	36	56
113	HFXBT12	209368 10/16/97	Lambda ZAP II	123	1378	1	1378	79	79	248	1	18	19	66
114	HNGJF70	209368 10/16/97	Uni-ZAP XR	124	1146	1	1146	94	94	249	1	16	17	45
115	HATEE46	209407 10/23/97	Uni-ZAP XR	125	1675	136	863	241	241	250	1	21	22	53
116	HJMBN89	209407 10/23/97	pCMVSPORT 3.0	126	1064	306	1064	348	348	251	1	13	14	56
117	HNHEK61	209407 10/23/97	Uni-ZAP XR	127	1607	1	1607	45	45	252	1	24	25	41
118	HEQAO65	209407 10/23/97	pCMVSPORT 3.0	128	1037	5	1037	152	152	253	1	27	28	160
119	HFCDV54	209407 10/23/97	Uni-ZAP XR	129	1146	1	1146	27	27	254	1	29	30	50

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
120	HHEAD14	209407 10/23/97	pCMVSPORT 3.0	130	1172	1	1172	53	53	255	1	18	19	278
121	HGBHE57	209407 10/23/97	Uni-ZAP XR	131	663	1	663	14	14	256	1	19	20	68
122	HGLAF75	209407 10/23/97	Uni-ZAP XR	132	776	1	776	231	231	257	1	28	29	121
123	HHEMQ28	209407 10/23/97	pCMVSPORT 3.0	133	1543	286	1543	442	442	258	1	31	32	58
124	HMWEC56	209368 10/16/97	Uni-Zap XR	134	2157	1013	2146	1067	1067	259	1	17	18	67
125	HERAR44	209407 10/23/97	Uni-ZAP XR	135	420	1	420	60	60	260	1	40	41	45

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

- 5           The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources
- 10       using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

### **Signal Sequences**

- Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch,
- 15       Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1
- 20       indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra.*) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

- In the present case, the deduced amino acid sequence of the secreted polypeptide
- 25       was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results
- 30       shown in Table 1.

- As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., +
- 35       or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

### **Polynucleotide and Polypeptide Variants**

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions,

5 interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be

10 determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and

15 subject sequences are either both nucleotide sequences or both amino acid sequences.

The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window

20 Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity.

25 For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of

30 the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are

35 considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired  
5 residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence.  
10 This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query  
15 sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or  
20 activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in  
25 the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.  
30 Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be  
35 deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

### Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-

60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred.

- 5 Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic  
10 regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide  
15 fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.  
20

### **Epitopes & Antibodies**

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an  
25 epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)

30 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to  
35 about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

20

### **Fusion Proteins**

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the

polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

### Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods  
5 In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography,  
10 phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also  
15 be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production  
20 procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein  
25 after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

### 30 Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome  
35 identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat

polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be  
5 selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the  
10 polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome  
15 specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al.,  
20 "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides  
25 correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage  
30 analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease  
35 could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined.

First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying

personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

5           The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set  
10 of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

          Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as  
15 tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more  
20 restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

          There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of  
25 unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

30           In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using  
35 DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

5 A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known 10 in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

15 In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for 20 NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ , 25  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human 30 subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson 35 Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the

proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders  
5 may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in  
10 treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to:  
15 blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also  
20 be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet  
25 disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in  
30 treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the  
35 present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

#### **Hyperproliferative Disorders**

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect

interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

### **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes

Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue

regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate  
5 nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral  
10 neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

#### 15 **Chemotaxis**

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of  
20 hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system  
25 disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present  
30 invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

#### **Binding Activity**

35 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit

(antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (c) determining if a biological activity of the polypeptide has been altered.

### **Other Activities**

10 A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

20 A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

25 A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

35 Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of

positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous  
5 nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of  
10 contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
15 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide  
20 sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a  
nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the  
25 position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under  
30 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which  
35 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type

Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as  
5 defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type  
10 of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel  
20 is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number  
25 shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a  
30 polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table  
35 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide  
5 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

10 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

15 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid  
20 sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human  
25 cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an  
30 individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of  
35 illustration and are not intended as limiting.

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

5            Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For  
10            example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
20	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

             Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are  
25            commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer  
30            sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

35            Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain

DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue,  
5 Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the  
10 corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone  
15 identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited  
20 sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported.  
25 The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as  
30 those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to  
35 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is

used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

5

**Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

10

**Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

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Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

25

**Example 4: Chromosomal Mapping of the Polynucleotides**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on

30

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either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

5 **Example 5: Bacterial Expression of a Polypeptide**

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as  
10 BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site  
15 (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses  
20 the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml).  
25 The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

30 Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from  
35 QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high

affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed  
5 with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The  
10 recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer  
15 plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a  
20 neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and  
25 XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or  
30 Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

35 **Example 6: Purification of a Polypeptide from an Inclusion Body**

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell  
5 culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a  
10 high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M  
15 NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

20 Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

25 To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted  
30 with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem

columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column  
5 volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above  
10 refolding and purification steps. No major contaminant bands should be observed from Commaassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### 15 **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus  
20 (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The  
25 inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as  
30 long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the  
35 AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring

signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures,"

5 Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

10 The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

15 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

20 Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the plasmid are mixed in a sterile well of a  
25 microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm  
30 tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life  
35 Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture

and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

#### **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

5           The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and  
10       Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a  
15       chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the  
20       CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse  
25       DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol  
30       outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially  
35       available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M; 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

5 For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that  
10 the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a  
15 heterologous signal sequence. (See, e.g., WO 96/34891.)

#### Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCC  
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAC  
20 CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT  
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG  
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC  
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG  
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC  
25 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT  
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT  
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA  
GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG  
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA  
30 GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC  
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC  
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

#### **Example 10: Production of an Antibody from a Polypeptide**

35 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera

containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

5           In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., *Nature* 256:495 (1975); Köhler et al., *Eur. J. Immunol.* 6:511 (1976); Köhler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell*  
10 *Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at  
15 about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

          The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line  
20 (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

25           Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a  
30 mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific  
35 antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in

Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a  
 5 control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of  
 10 cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM  
 15 with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of  
 20 Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml  
 25 of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0  
 30 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319  
 35 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine;

0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- $\alpha$ , IFN- $\gamma$ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>		<sup>252</sup> <u>STATS</u>	<u>GAS(elements) or ISRE</u>
			<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	
<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3 ISRE
	IFN-g		+	+	-	1 GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3
<u>gp130 family</u>						
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3 GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrohic)	?	+	?	?	1,3
	OnM(Pleiotrohic)	?	+	+	?	1,3
	LIF(Pleiotrohic)	?	+	+	?	1,3
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3
	IL-12(Pleiotrohic)	+	-	+	+	1,3
<u>g-C family</u>						
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5 GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6 GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5 GAS
	IL-9 (lymphocytes)	-	+	-	+	5 GAS
	IL-13 (lymphocyte)	-	+	?	?	6 GAS
	IL-15	?	+	?	+	5 GAS
25						
<u>gp140 family</u>						
30	IL-3 (myeloid)	-	-	+	-	5 GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5 GAS
	GM-CSF (myeloid)	-	-	+	-	5 GAS
<u>Growth hormone family</u>						
35	GH	?	-	+	-	5
	PRL	?	+/-	+	-	1,3,5
	EPO	?	-	+	-	5 GAS(B-
	CAS>IRF1=IFP>>Ly6)					
<u>Receptor Tyrosine Kinases</u>						
40	EGF	?	+	+	-	1,3 GAS (IRF1)
	PDGF	?	+	+	-	1,3
	CSF-1	?	+	+	-	1,3 GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCG  
10 AAATGATTTCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCGAAATG  
20 ATTTCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCC  
CTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTTCTCCGC  
CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGC  
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT  
TGCAAAAAGCTT:3' (SEQ ID NO:5)

25 With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase,  
30 alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter  
35 element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning  
5 site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules  
10 containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter  
15 construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

**Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors,  
20 such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and  
25 Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately  
30 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to  
35 generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final  
5 concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

10 On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

15 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12  
20 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples  
25 from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

30 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

35 **Example 14: High-Throughput Screening Assay Identifying Myel id Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the  
5 Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with  
10 PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM  
15 KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400  
20 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-  
25 well plate (or  $1 \times 10^5$  cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the  
30 protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

When cells undergo differentiation and proliferation, a group of genes are  
35 activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon

activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or  
5 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

10 The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

15 Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

20 To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker)  
25 containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

30 Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

35 To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count  
5 the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR  
10 can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

15 NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-  
20  $\kappa$ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-  $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I-  $\kappa$ B is phosphorylated and degraded, causing NF-  $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target  
25 genes. Target genes activated by NF-  $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating  
30 diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5 5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)  
Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

15 5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCA  
TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTTCTCCGCCCCATGGCTGACT  
AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTC  
20 CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:  
3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and HindIII.

25 However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the  
30 NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described

in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

- 5 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

- 10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15  $\mu$ l of 2.5x dilution buffer into Optiplates containing 35  $\mu$ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

- Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50  $\mu$ l Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50  $\mu$ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

- 20 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25

28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is

incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

#### **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating

tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately  
5 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from  
Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with  
100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr  
with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine  
(50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or  
10 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed  
with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000  
cells/well in growth medium and indirect quantitation of cell number through use of  
AlamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento,  
CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are  
15 used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture  
plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of  
Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium.  
Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20  
20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example  
11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH  
7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>  
and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim  
(Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for  
25 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract  
filtered through the 0.45 mm membrane bottoms of each well using house vacuum.  
Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum  
manifold and immediately placed on ice. To obtain extracts clarified by centrifugation,  
the content of each well, after detergent solubilization for 5 minutes, is removed and  
30 centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many  
methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by  
determining its ability to phosphorylate a tyrosine residue on a specific substrate (a  
35 biotinylated peptide). Biotinylated peptides that can be used for this purpose include  
PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2+</sub> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.  
15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and  
20 incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

## 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be  
30 used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by  
35 substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

#### **Example 21: Method of Determining Alterations in a Gene**

##### **Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR

products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., *Nucleic Acids Research*, 19:1156 (1991) and sequenced with T7  
5 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-  
10 triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., *Methods Cell Biol.* 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and  
15 propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., *Genet. Anal. Tech. Appl.*, 8:75 (1991).) Image collection, analysis and  
20 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated  
25 disease.

#### **Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is  
30 a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with  
35 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

### **Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., *Biopolymers* 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and R. Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

#### **Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

**Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

**Example 26: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

5 The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the  
10 presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue  
15 culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

20 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media  
25 from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

30 The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and,  
35 therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other

disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:  
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and  
(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Rosen et al.  
Human Genome Sciences, Inc.

<120> 125 Human Secreted Proteins

<130> PZ020.PCT

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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1547)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1549)  
 <223> n equals a,t,g, or c

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5

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&lt;210&gt; 13

&lt;211&gt; 1589

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

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&lt;210&gt; 14

&lt;211&gt; 1255

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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&lt;210&gt; 15

&lt;211&gt; 1191

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 15

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&lt;210&gt; 16

&lt;211&gt; 1186

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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&lt;210&gt; 17

&lt;211&gt; 1182

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 17

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&lt;210&gt; 18

&lt;211&gt; 1171

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 18

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8

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&lt;210&gt; 19

&lt;211&gt; 1337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1318)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 19

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taagtaatcc	agccttt					1337

&lt;210&gt; 20

&lt;211&gt; 1162

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

9

&lt;400&gt; 20

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&lt;210&gt; 21

&lt;211&gt; 1837

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

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&lt;210&gt; 22

&lt;211&gt; 1054

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

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&lt;210&gt; 23

&lt;211&gt; 1066

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 23

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12

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13

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&lt;210&gt; 29

&lt;211&gt; 1466

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

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&lt;210&gt; 30

&lt;211&gt; 1226

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

14

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&lt;210&gt; 31

&lt;211&gt; 1094

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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atttcttcct	tatagttatg	gctcatagag	atgactgctc	tttcaaaggt	ggttgtgggc	120
tattagagcg	tttccaatgt	ccccatactt	ctttctcgag	tgctagtcaa	aagcgacttg	180
cagatgggtat	ggaatgtctt	tgtgagatag	aaagaacaca	gactaggatc	agaaaaatct	240
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aatagcctcca	cacctacctg	ccaggattgt	cttcagaatt	acataaaaata	acacatacca	360
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gtaactaggt	cacttggtaa	tttcaatttc	agacgtaaat	ttttctgtgt	ttcagaatta	960
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aaaaaaaaaa	aaaa					1094

&lt;210&gt; 32

&lt;211&gt; 1037

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

15

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 32

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gagtcgcccc	acaagaagaa	gaaaatcgcg	gcccggagga	aatgggaggt	gttcccggga	120
agaaacaagt	tcttctgtaa	cgaggaggatc	atgatggccc	ggcagacggg	cgtcttctac	180
ctgacgctcg	tcctcatcct	ggtcactagc	ggactcttct	tcgccttcga	ctgtccgtac	240
ctggcgggtga	aaatcacccc	tgccatccct	gcagtcgctg	gcacccctgtt	cttctttgtg	300
atggggaccc	tgctccgcac	cagcttcagc	gaccccgag	tcctccacg	agccacacct	360
gatgaagccg	ccgatctgga	aaggcaata	ggtaacactg	aaagtctgcc	catggcctct	420
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caggatgagc	tgaagaagag	gtgtgatata	aggctggagg	gacaggtatc	ctggaggcag	600
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acccaagtgt	ttgattccac	tctactaagc	agcctccacc	ccgagagatt	acagttgtag	720
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tccttagata	ttaaaacct	tactaaagtt	tattacaacc	cattttgaag	atattaaaac	960
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aaaaaaaaaa	actcgag					1037

&lt;210&gt; 33

&lt;211&gt; 1376

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 33

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acatgctctc	cctctttggc	actggagcta	ttctgatgcg	tggaagcaggc	tgtactatta	240
atgacatgtg	ggaccaggac	tatgataaaa	aggttacaag	aacagccaat	cgtccaatag	300
ccgctggaga	catttcaact	tttcagtcct	ttgtttttct	tgggggacag	ctaaccctgg	360
cactgggtgt	tcttctgtgt	ctaaattact	acagtatagc	tctgggagca	ggatccctac	420
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&lt;210&gt; 34

&lt;211&gt; 1220

<212> DNA  
 <213> Homo sapiens

16

<220>  
 <221> SITE  
 <222> (803)  
 <223> n equals a,t,g, or c

<400> 34  
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 gggaagggag tccgagaacc ctcttcgttg actcaacttc ccaggcttct gtccctgctg 180  
 cagaatgccc aggccacaga gaagggaccc ccttttcagg agcttccacg tcacaggctt 240  
 ttatggggcc tttcttgctt gtgtttctgt ttcccatcct gaggggtgtgt ggaataatac 300  
 gagagcctac ccaggactgg agcgtgttat tagaaagagc acgcttgact gctcccgggc 360  
 agccacctgc cctttttccc ttggaaagtg gacctatggc cactgcacaa aacacttcct 420  
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 ttattgttat tatttttctt ttaaagtgtc taaaagtgc cagcttgtgc aagtggagtc 600  
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 aagacaggct ctcatattt actgcttgta tttatataat ggaagttagg taacataagc 720  
 ccctctgcag gccagcttag atgttgatga tgcttaaagt gtaaaatctg tgagaatgtt 780  
 caacaatgcc ctgtatttgt acngcctaaa actgaataat acatatgtga catgaataaa 840  
 taggtcagtg atttttatga catattaatt tcctttacct aagttcctgg gaaatatagc 900  
 tgaacagtta cagagaatga aaacaaacac tggcatctta caaacacctg ctttgattat 960  
 ttagtctaata taggttaaat ttaactattt ccattttaac aaattgaaaa caattcttat 1020  
 ctgttcctcg gtcatgcact ttatcagtg tggatgcaga tgtgtttaat atgacacagt 1080  
 tgggtgctgt ttctcagctc tgggtgggaa ataaaaagga attgagaaca tattttttaga 1140  
 gtcttctggg gactttgtat ttctgggcct atagctatga aattttaagg aggaggaaaa 1200  
 aaaaaaaaaa aaaactcgta 1220

<210> 35  
 <211> 1346  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (537)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (880)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1115)  
 <223> n equals a,t,g, or c

<400> 35  
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 tgccaggagt aatgtgtctc catagtactc tgatccactt gtatttggtg cttecttttt 120  
 tttttctttt ccttccctcc tcctttcctt tcccttctty ttcctsttcc tccattcttc 180  
 cctccctccg tcttccctca ttcttccctc cctccctatt cctccattct tccctccctc 240  
 cctccctctc acatccttta ggactcagca tcacctcctc taggcagctt ttcttggayt 300

17

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actggttatt	gccttgaggg	gatgacaact	gcccggtagg	gtwacctggg	gtgactgcac	480
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cttgaggaac	tctaaggccc	ctactgtgca	ggtcttatta	atgattacaa	cagcagcagc	660
agccagtgtt	tactgaggac	ttacaaagca	ccaagcactt	tgccatcct	aatccttaca	720
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tttaaaaaaa	aaaaaaaaaa	actcga				1346

&lt;210&gt; 36

&lt;211&gt; 1026

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 36

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tttgtagect	tcactgttgg	ctgtctccat	ggcaggtgag	ctgcgacctt	ttgtcagcag	120
cctagctgag	atggctgctg	atgcctgcag	gtataagtga	ctgtcaattt	tccttactca	180
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tcaatctatc	atgtttgcct	aattttgtct	ttgtacatca	catctcacag	tcaccagaac	300
atgagtagct	gtctccaggt	gcctctgtct	ctgttatctt	gcccactgaa	gggagagcac	360
ttaagccaat	ttgcaggaga	ccacagtttg	ccagagggtca	gagacagaaa	tcaccactgc	420
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tgcgta						1026

&lt;210&gt; 37

&lt;211&gt; 832

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 37

gctataacca	accatgctag	caaacttcac	actgttcatt	ctgactctaa	tatcttttct	60
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tcaagatctc	agcaccaagg	tccatataaa	acctttgcaa	actgttatct	ccttccttat	180
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gagcaatctt	gtattcctgc	tttaccaaac	tcttgcaatc	atgtatcctt	cattccactc	300
attcatcctg	attatgagaa	gtaggaagct	aaaacagacc	tctctttcag	ttttgtgtca	360

18

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&lt;210&gt; 38

&lt;211&gt; 706

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

ggcagaggtg	acaagccccg	ccaagacaga	cctgcaagtc	ttcgtctcaa	gggacctccc	60
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&lt;210&gt; 39

&lt;211&gt; 1347

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (83)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (334)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 39

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19

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aaaaaaaaaa	aaaaaacccg	cacgtag				1347

&lt;210&gt; 40

&lt;211&gt; 1467

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 40

gaattcggca	cgagcagagc	aagactccaa	ctcaaaaaaa	ataaaaagaa	agaaagaaac	60
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&lt;210&gt; 41

&lt;211&gt; 914

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

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tctccaatct	gcgctgtggc	acaccagaag	agccctgtca	ggaggccttc	aaccaaacca	300
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20

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cccatactc	acctcttttc	attttgagta	ataaatgtct	gagtctgaaa	aaaaaaaaaa	900
aaaaaaaaaa	aaaa					914

&lt;210&gt; 42

&lt;211&gt; 1131

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 42

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gtggcgattt	ggaatcctct	cgatctgcat	gctctgtgtt	ggactagtgc	tgggggttct	180
catctcgtca	gtgactttct	ttactccact	gggaaaccta	aagatttttc	atgatgatgg	240
tgtattctgg	gtcactttct	cttgcatagc	tatcctcatt	ccagtgtttt	tcattgggctg	300
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tccattaaat	agatacatta	aaaaaattaa	aaactgaatt	cttctgtcag	aaaaaaaaaa	1080
agaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	a	1131

&lt;210&gt; 43

&lt;211&gt; 1333

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (411)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1264)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1319)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 43

21

cctggaacac	ttcaacaacc	agtatccagc	cgagagggcg	gtgaactttg	gcacctgggt	60
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tggtgtccct	gagcagcctc	ccaccgtggg	ctgtcaccct	gctggcatgc	atcctcgtgt	660
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gcagcctgtc	tgaacgctg	cacattaacc	ccctctacac	cctgatccca	gtcaccatgt	780
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tggtgatagt	aatgggtggc	atcaacacct	ggggagttag	cctcttccac	ctggacactt	960
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caanccatag	gtccacaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaana	1320
aaaaaaaaaa	aaa					1333

&lt;210&gt; 44

&lt;211&gt; 1004

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 44

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aagtcgcagt	gagccgtgat	catgccattg	cacccagcc	tgggcaaaaa	gagcgaaact	960
ccatctcaaa	aaataaaaac	aaaaaaaaaa	aaaaaaaaact	cgag		1004

&lt;210&gt; 45

&lt;211&gt; 1494

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 45

>>

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&lt;210&gt; 46

&lt;211&gt; 1166

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 46

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&lt;210&gt; 47

&lt;211&gt; 1536

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

33

&lt;400&gt; 47

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&lt;210&gt; 48

&lt;211&gt; 1038

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

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gtgctttag	taaatgaagg	ttggatggat	ggatactgac	aatgggtggca	ggcatttcaa	180
gcctttttaa	ttagtacttt	ttgtcgtctt	gcttattaaa	attttgttaa	ttttagcaaa	240
gaccaattgt	tgtgataaac	tgggtgtttt	tggatgcttc	aagcacacgt	taaccaattt	300
tttaattccc	cttttggttc	ctcccattgt	tctaaaatag	gactttcata	ttattaaaac	360
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aaaaaaaaaa	aaaaaaaa					1038

&lt;210&gt; 49

&lt;211&gt; 1176

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

H

&lt;400&gt; 49

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&lt;210&gt; 50

&lt;211&gt; 731

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

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aaaaaaaaaa	a					731

&lt;210&gt; 51

&lt;211&gt; 1437

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

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25

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&lt;210&gt; 52

&lt;211&gt; 1369

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 52

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gacagtagag	tccttgattt	actgtcccat	ggccctgct	catcttctct	ttcttgattg	480
atggtgccat	catctaccca	gttactttga	ccaaagcaat	gggagtcac	ctggattcct	540
tkcttcttct	ccacttctaa	gccatcagta	tactggcact	gtgttaaagc	catatttcaa	600
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ctagcaggca	ctggagccta	tttctggaat	ttcatgttgc	accattgccc	tctctgtttg	1260
ttctccatta	ctaaattcct	ttcaagccaa	ccccatggcc	tccatgactt	tttcaaaaaa	1320
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaactcga		1369

26

<210> 53  
 <211> 1037  
 <212> DNA  
 <213> Homo sapiens

<400> 53  
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 ttccaccttc ttgtggctgc tggcattctt tggcttgtgg tcacatcact cctatcttga 180  
 aggccagcat cttcaaattct gtttcttctt cacatagcct tctgtgtgtg cagtgccttc 240  
 tacctctctc ttataaagac atttgtgatt aaatggaggg tttaggataa tctcgtcaag 300  
 atccttaact taatcacaac tgcaaaaacc tctttcccaa ataaggtaac attcacaggt 360  
 tccagggatt aggacctatt atcttttggt agtattatc agcctaccac aatagctaaa 420  
 acaattctga aaaagaagaa taaagtgaga gaaatcagtt tatctgattt cgatacttat 480  
 tgtatagcta tggtaaataa ggctgcatgg tattaagaa aggacatata tgaatgaaac 540  
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 agaagacaat ttattggagg aaagacagcc ttttcaacaa atgggtactat aacaattaga 660  
 tatccatagg caaaaaaaaa aaaaagaatc ttgatctaag gtcacacct tatataaaat 720  
 aatattaaac tcatggccag gcacagtgc tcatgcctat aatcccaata cactgggagg 780  
 ctgaggcaag agtatcactt gaggccaggg gttcaagact agcctgggca acacagtga 840  
 actctatctc tacaaaaaaaa ttataaacta gctgggcatg gtggcacatg cctgtagtca 900  
 caactactca cgaggctgag aagatcactt aagctgagtt gttcaaggtt ctaatgagct 960  
 acaatcgtgc cactgcactc cagcctaggt gacagacaaa gaccccatct caaaaaaaaa 1020  
 aaaaaaaaaa actcgta 1037

<210> 54  
 <211> 1373  
 <212> DNA  
 <213> Homo sapiens

<400> 54  
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 tggtttgtgt tgtgtgtcag ggcgcagggg tttctgcttt cactcaagtt aatttatattt 180  
 ccttttctt ggtaattgtg aaaaaacaaa ataaaacctc ctgtgagcct tttggaactt 240  
 ctggaaaagt ccttttgctg tgarcsgctg actctgagaa gagctttgag cagggtcgga 300  
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 acaaaaatcc tctccttac ytctaattac aaagaggaaa aagtcactga aaaaaaagt 540  
 ttaaaatgtc ttaataataag agtcatatat aatccaaagc taccaaaggc caagtgttta 600  
 gggggaagtt tctggtggtt aacccactt cagggggatt taaagtgggt gtggtgagga 660  
 tttggtcca ggtatgcgtc ctgccaacct ggggtgggtg tccctttggt ggagcctctt 720  
 gaaaaatgar ggartggctg ggtgcagtgg ctcatacctg taatcccasc actttgggag 780  
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 aaaaaaaaaa aaaaaagag ggagtggctg ggtgcagtgg ctcatgcctg tatcccagca 1080  
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 aggtcgcagt tagccatgat tgtacctctg tacgccagcc tgggtgacaa agcaagagcc 1320  
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<210> 55

&lt;211&gt; 1347

27

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 55

ggcacgagct	ggtctatagt	gaagttactg	gccattccaa	aggctatgga	tttgtggaat	60
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catcagcact	ctttgcacaa	tgatgggatg	ttaatctatt	ggcttcagag	ctcattcatt	180
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&lt;210&gt; 56

&lt;211&gt; 822

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 56

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agttcagaat	gccaaaacgt	ttctggTTTT	atttgtcttg	ggtgaggacc	cagaggggtg	120
ggagatggag	gtgtgagcag	catgggtctgt	tgtggTTTTt	tcttgttggtg	gagtagagtt	180
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&lt;210&gt; 57

&lt;211&gt; 536

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

<221> SITE  
 <222> (536)  
 <223> n equals a,t,g, or c

28

<400> 57  
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 ctgtcccgtg accaaactcc tctctgtccc cagctggact cctctagatg ctcagatgct 120  
 ccttctcttc tttccttctc tgtcacacca ttcttctgtt ccttggctct tctgctcatc 180  
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 ccagggttga ggggtggggcc tttgctagggt aaccaccctc ttctaccag tattttcctg 360  
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 tgaaatggga aatgcaagggt ataaaggaga attgctgtcc ttgaaaagaa atttagtttg 480  
 tttttttgtt gagatggagt cttgctctaa gctagagtgc agaattgtaat caaggn 536

<210> 58  
 <211> 1262  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (12)  
 <223> n equals a,t,g, or c

<400> 58  
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 ccaagtgtat atagattcag tgcttatttc tcagcttttt ctttcttaag ttcattctctg 360  
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 cc 1262

<210> 59  
 <211> 1269  
 <212> DNA  
 <213> Homo sapiens

<400> 59  
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&lt;210&gt; 60

&lt;211&gt; 1829

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 60

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3

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1829

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 <211> 1112  
 <212> DNA  
 <213> Homo sapiens

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<210> 62  
 <211> 1674  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (734)  
 <223> n equals a,t,g, or c

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gacaggacct ggctgttggt tctctctgac ctaacagga tttatgccct gcatccgcgg 180
tgtttttcac tgttttattc ttattattct tattctcttg gcgtcacatg cgttttagtg 240
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tgagccaggg tctgccaatg ccacttcagc ctarggctg agctgggcct ggagaggaaa 480
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31

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&lt;210&gt; 63

&lt;211&gt; 1045

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 63

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&lt;210&gt; 64

&lt;211&gt; 1051

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

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 aatgatatca cttgaaggta gactgtgata agttaaatac gtatatattt taaatcttca 960  
 aacaaccact aaaataaaaag aacaaaagag tacaactaaa aaaaaaaa aaaaaactac 1020  
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&lt;210&gt; 65

&lt;211&gt; 1182

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

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 attaagtggg tctcatctct aaaaaaaaaa aaaaaaaaaa aa 1182

&lt;210&gt; 66

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

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&lt;210&gt; 67

&lt;211&gt; 1105

<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
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<223> n equals a,t,g, or c

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<212> DNA  
<213> Homo sapiens

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34

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 <211> 1638  
 <212> DNA  
 <213> Homo sapiens

<400> 69  
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<210> 70  
 <211> 887  
 <212> DNA  
 <213> Homo sapiens

<400> 70  
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887

<210> 71

<211> 864

<212> DNA

<213> Homo sapiens

<400> 71

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<210> 72

<211> 1217

<212> DNA

<213> Homo sapiens

<400> 72

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<210> 73

<211> 1717

<212> DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (712)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (721)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (903)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 73

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&lt;210&gt; 74

&lt;211&gt; 1276

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 74

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37

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&lt;210&gt; 75

&lt;211&gt; 1144

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

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cgta						1144

&lt;210&gt; 76

&lt;211&gt; 918

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

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39

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ataaaaaaaaa	aactcgag					918

&lt;210&gt; 77

&lt;211&gt; 1065

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

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&lt;210&gt; 78

&lt;211&gt; 1126

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1124)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 78

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39

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&lt;210&gt; 79

&lt;211&gt; 984

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (232)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (332)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (333)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (929)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (943)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 79

tcgaccacag	cgctccgcgcg	tccgtcgggtc	ggtgcgtccg	ggccgcgggc	ttcgmcctcg	60
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40

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&lt;210&gt; 80

&lt;211&gt; 1247

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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tgcagacaga	agtatgccct	catggaactc	tcacctccag	gggttcccct	tagacctcac	120
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gttggaaggc	gggatgcttt	gtgccccttc	cagcaagcta	acttccaaat	aaattctcta	300
wttttatata	agaccttgtt	cttgtaatt	agactttaca	tgaagtgagc	aactaagctt	360
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&lt;210&gt; 81

&lt;211&gt; 946

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 81

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cagttgaagt	tgagacatga	atctctgcat	gtaggggaaa	ttttgtgtct	ggttagtcaa	120
gaaactatgg	aaaccaattc	ttgatatttt	gaaccattca	cgaagatagt	ttgagtcatg	180
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aggtcggaat	gaaacattta	caaaaattga	catttcttta	tgcatagata	tttactagg	900
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<210> 82  
 <211> 1392  
 <212> DNA  
 <213> Homo sapiens

<400> 82  
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 cagatgtctc tatgattaat ttttggcctg tctactcatgt ttgcatatgg ctgttggtggc 180  
 tccaagcatt ggaagcaaga ggacagggaa gcaacattga ctgtaccagg aactccaaaa 240  
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 tggggacaag atagtggtaa ggattagatt tggccagaaa gtttctgcca cagtgaagctt 360  
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 tactgttggg tacaattatg aaaccaactt gaatactttt tagttgaaca tttcagtagt 480  
 cttaattatg tttaaatagg tttcacaatt tactgttttt agtttagttt cgggctcccc 540  
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 cagaactaat tatgcaagtc ttcatttagc tttttaaaaa aacagcttta ttgagttaga 720  
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 ttttcggcac ga 1392

<210> 83  
 <211> 1155  
 <212> DNA  
 <213> Homo sapiens

<400> 83  
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 atgtgtgtat atacacacat atatgtacat atatttaata catttggtga tgtgtgtgta 180  
 tatatatata tatatacttc tcattattta tactctagac ccagagcctc ctagctgggc 240  
 tccaaaattg gactctcatc tctctttgag acagccttca aatgatcggt tttaaagtgc 300  
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12

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aaaaaaaaaa	aaaaa					1155

<210> 84  
 <211> 1373  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (877)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (897)  
 <223> n equals a,t,g, or c

<400> 84

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<210> 85  
 <211> 1258  
 <212> DNA  
 <213> Homo sapiens

<400> 85

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43

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&lt;210&gt; 86

&lt;211&gt; 1318

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 86

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&lt;210&gt; 87

&lt;211&gt; 978

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (977)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 87

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44

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aacaaatgaa	aataaatatt	aattttataa	tatgggaaaa	aaaaaaaaaa	agggcggccg	960
gtaaccatt	gcgcccna					978

&lt;210&gt; 88

&lt;211&gt; 1863

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (112)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 88

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45

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&lt;210&gt; 89

&lt;211&gt; 2086

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 89

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&lt;210&gt; 90

&lt;211&gt; 891

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 90

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&lt;210&gt; 91

&lt;211&gt; 1974

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (654)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 91

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47

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&lt;210&gt; 92

&lt;211&gt; 1423

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 92

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&lt;210&gt; 93

&lt;211&gt; 1365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 93

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48

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&lt;210&gt; 94

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 94

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&lt;210&gt; 95

&lt;211&gt; 938

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (479)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 95

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49

938

<210> 96  
<211> 928  
<212> DNA  
<213> Homo sapiens

<400> 96  
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<211> 1715  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (17)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (34)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (40)  
<223> n equals a,t,g, or c

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50

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&lt;210&gt; 98

&lt;211&gt; 678

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

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aaaaaaaaaa	aaaaaaaaaa					678

&lt;210&gt; 99

&lt;211&gt; 1541

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

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51

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&lt;210&gt; 100

&lt;211&gt; 881

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 100

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&lt;210&gt; 101

&lt;211&gt; 947

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 101

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52

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&lt;210&gt; 102

&lt;211&gt; 1369

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 102

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&lt;210&gt; 103

&lt;211&gt; 1231

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 103

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53

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&lt;210&gt; 104

&lt;211&gt; 1242

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (288)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 104

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&lt;210&gt; 105

&lt;211&gt; 1151

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

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54

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&lt;210&gt; 106

&lt;211&gt; 1628

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 106

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&lt;210&gt; 107

&lt;211&gt; 1465

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 107

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ataaatataa	taattgagag	gtctgcatta	gatgtggcag	ggagaacaag	caaaaagaga	180
tttcagagaa	gatcactgga	attggcagag	gccttgaagg	gcagagtcta	gcatacagaa	240

55

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cacatgggtc	agtaatgccca	ttgaaaaaca	aaatttttaga	ctaagtgggg	tcgcagaaat	720
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gagcttgaaa	agctacttca	aaaaataaat	tctaggccag	gtgtgagyc	atgcgcttga	1440
ttaaaaaaaa	aaaaaaaaac	tcgta				1465

&lt;210&gt; 108

&lt;211&gt; 1265

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (766)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 108

ggggcagatg	gaaatgtctc	ggattttgat	aatgaagaag	aggaacagtc	agtccctccc	60
aaagtggatg	agaatgacac	ccgtccagat	gtggagccac	caactgccatt	gcagatccaa	120
atagccatgg	acgtgatgga	acgtgcatc	cacttggtgt	cagataaaaa	tctgcaaatc	180
cgctgaagg	tcttgatgt	gctggatctg	tgtgtggttg	ttcttcagtc	ccacaaaaac	240
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ttagaaatgg	attgaaggaa	agtagctgac	tattatttat	atttcatacc	ttgtgttttc	1020
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acacctccct	gtcttcaaat	aatgagatgg	aactaatttg	ttttacctaa	cctgatcttt	1200
gggaaacaaa	cggaataaaa	gacacttctt	ggatgaaaag	taaaaaaaaa	aaaaaaaaac	1260
tcgag						1265

56

<210> 109  
 <211> 1006  
 <212> DNA  
 <213> Homo sapiens

<400> 109  
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 ctatagtgat aggcgtttat acatttcccc tttagccat ttctttatga acagtgggtc 180  
 ttctgtctca agtgttctgt ctcatcttta tgtttctcaa atcttcttta aaaatgtaag 240  
 caaatatttt taaagaattt ttatgttttc caaaattagg atttttagact ttagggattt 300  
 tgatcttttg ggatttcaac attcgggatt atgggtgttca gtgtgtattt tggggggatt 360  
 atgatcagca tcccatacag tggaatatca tttggcaata aaaaggaatt aaatattgat 420  
 tcatgtctaca acatggtgaa cctaaaaaac attatgttca gtgaaagaag ccaaacctaa 480  
 aaggcctacg tactgtgttg ttaaattggt aaaatggtga atttatcaca atcaaaacca 540  
 ataaacctct acaggaaaaa ataaggacaa agaaaggctg ttccctatta atggagacta 600  
 aagagacatg acaactaaat gcagtttatg attgtggatt acatccttga tcaggggtgaa 660  
 aatagctata aaggaaatta ttgggacaat ttgctaaaat ttgaaaatgg actggatttg 720  
 gctggctgca gtggcttaca tctgtaatcc cagaactttg ggaggccaag gtgggtggat 780  
 tacctgaggc caggagtcca agaccagcct ggccaacatg gcaaaaccgc tctctactaa 840  
 aaatacaaaa attagatggg cgtgggtggg tgcattctga atctcagcta ctcgggaggc 900  
 tgaggcttga acccgaggag cagaggttgc agtgagctga gatcacgcta ctgcattcca 960  
 gcctgggtga cagagcgaga ctccatctca aaaaaaaaaa aaaaaa 1006

<210> 110  
 <211> 1258  
 <212> DNA  
 <213> Homo sapiens

<400> 110  
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 tataccttgc cctctatcat tataaatggt tgccatgggt ttcttaaaaa taagtgtttt 180  
 accattaatg tgtagagggc aaacaaagca taaagtacta agggatcatg cttatcctag 240  
 ggtctcacag aagagaggac atattttaatt aatcttgtga attacagaac aggttgtggg 300  
 ccagacacca agaatcatag gggttttttt ttaaaaaacc taatagaagt aggggtgacct 360  
 ctctcttttg tctaagagtt ctaaaggaag gtaggcattt gtttaattag ttggttcacc 420  
 ctggcctttac ctctggttaa tgcttgtgtt aataggaagg aaaaatcact ttatcttttc 480  
 ttccaagccc ctccctgcct gacttaccga gactgggatt accagatacc aggtgattta 540  
 tgtggagatg atttttcacc tttaaactct aagccaagt taagaaactc ttgatagcta 600  
 tgtctatttt atatcagtca ctgagacttt tttttaagtt tttatttatt attaaagcaa 660  
 ctttgccaaa aaagtcctct aagcacaact atttacattt ctttatagcc tcttctgac 720  
 tctaacacat atgcagtttt aactgttatt ttcatagtaa ctgatctttt gtctaaggat 780  
 ttttacctga aagcacaatg tattgagtct cttgaaaatc atctttcaga tctttttaca 840  
 gaatgaactt atgcactgct actgtagtat tctcaaggaa tatatgtaaa cacaaatgta 900  
 tgcctgaggt tggtttttgc agaaaacagt ctctgcttct aaaaacttct atgtctagtc 960  
 ttccatagga aatcctcact gtttaaccat gtgaggagcc taagtcatta aacggatcat 1020  
 gtctgtacat tgtgtaatga atgaaaagca cataaatgta atctactttg aactttgtaa 1080  
 aaatgatgtg tggaggctat tcttgtttct ccattctcaag tctgtgtgt gcacgtgtgt 1140  
 gcaagtgcac atgtgtgtgt gtaataacac attgtaaga acagaaatta ctttaaaaaa 1200  
 taaacagaaa tggagacctg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 1258

<210> 111  
 <211> 1453  
 <212> DNA  
 <213> Homo sapiens

57

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (946)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 111

ggatcatcttt	ctcttgctcg	tacagagagg	agacacccgt	agaaatggag	atttctacta	60
cagatgaaaa	tttcttttat	aaaagggtaa	cttctctgta	ttatcctgtg	tttgctattt	120
ctgaaaataa	taagctgaaa	atattcctct	ttggcataag	gattatttgg	tgtggcatgt	180
tctgaacctc	cactgttggc	atcctttctt	gattagcaga	aacctaggaa	cattgttgta	240
ataatgacta	aattattgtc	actgtcacat	ttgttagtaa	ctttttttaa	tataattgcc	300
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cttgggtggtg	ggcgctgtg	atcccagcta	ccggggaggc	tgaggcagga	gaaaggcatg	1020
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acagagttag	actccatctc	aaaaaaamga	awaaaaaaa	caacttattt	taaattattt	1140
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atataatatt	ctcatacact	ttcttaggatg	ggatagatcc	ctgtaacaga	atattggtta	1320
acaagagaaa	aacaagtttt	aagacatgta	tacctcatat	atacatggga	gatactcggg	1380
ggaagttagt	aaatctctca	gaggtggcct	aaataccatc	atgtcctgaa	aaaaaaaaaa	1440
aaagggcggc	cgc					1453

&lt;210&gt; 112

&lt;211&gt; 1552

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1035)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 112

ttgcctaagg	cccactgtgc	caaattagat	aatacaagaa	gttcattttac	actgtagacc	60
agtgaagtca	atgactgttt	gctctgtgat	accgtttcaa	aaatccaaaa	tgcagacttt	120
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58

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&lt;210&gt; 113

&lt;211&gt; 1489

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 113

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gagtgaagca	acatggatgc	agtcagccaa	gtcccatgg	aagtcgtgct	tcccaagcac	180
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accactcaag	ctcttcgata	ccaaaatcag	gagcatcttg	ggatttatta	aattatgtaa	1320
gaagatagca	cagatatcgg	gatattattg	tgtgaaaatg	ctgctttttac	tttgatgtga	1380
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aaaactgcga	ggggggggacc	cgtaacccta	atcgacctta	atgagtgtga		1489

&lt;210&gt; 114

&lt;211&gt; 607

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 114

ggcacgagtt	tcaacttgag	atttggaggg	gacagacatc	caaaccgtat	cattaaattt	60
aatagtttta	tgcagttttt	ttggctctag	atctgttttag	actcctgcag	tcaggtgtct	120
gtaactagcc	tctggctcct	tttgagagtt	cacagtttgg	tgcaaacctt	ttggatgtat	180
tatttgggaa	aatgggatat	ctggcagcct	gtgtccctgc	tttacattat	cctttttgct	240

59

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ggcgcttcct	ccccagcacc	aggcttatgg	ttctaagctc	cagaaaaata	tcaaataaac	600
cctgccc						607

&lt;210&gt; 115

&lt;211&gt; 1498

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (791)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (895)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (915)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (936)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1017)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 115

gcatccccc	ttctgttcct	ggaccctctt	ctgtcacccc	atcgacaagt	aaagaaatca	60
agaaatccaa	actgattcga	agccagtctt	ttaataatca	agcttttcat	gcaaaatag	120
gcaacttaga	gaaatgtgct	agtaaaagtt	ctacaacagg	atatacaact	tctgtctcag	180
ggttaggaaa	gacttctgtg	ctttcactag	ctgatgattc	attccggact	cgtaatgcca	240
gtagcgttcc	atcttccttt	tctcctaata	ctcccttacc	gagtacttcc	cgtgggacag	300
gtaactcagt	tgaccccaag	agcagtggaa	gtaaagatac	acaaccacgg	aaggctacct	360
taaaatccag	aaaatccaat	ccttaaatca	actgcttgat	gaaggaggca	aaacaaaggc	420
agcaggagat	aatgtgattg	gtacacaaaa	gctaaagcag	tggctggggc	tttgttttta	480
aattttgggt	tttttttttg	ttgttggtta	tgagcagaaa	gagagacata	atgacagctg	540
atgttaaact	tttcatattt	caaattagat	tccctaggag	gtataatata	tatttcttga	600
gtaataatgt	ggttacggaa	ttccaatggt	atagtgaagt	gtaatgaaaa	acatctctag	660
gaatgtgctt	taaccactgc	tgcaaaagar	acaagtctgc	atttatttgt	gcaggaaacc	720
accatttaat	tgttctagar	tttttagcatt	taaaaatcgt	atgaaagtct	acatcagctg	780
aattgtccta	ncttgataag	cacttggagg	gggacttgga	aggtgagaaa	gatactgcat	840
tttctcatga	gtctccaagc	ccacttgaaa	agtcacactg	aaaggatgca	aatancogtc	900
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atttaaattt	ggcagtgraa	attccacaaa	gatttctggt	aacttkgagc	tataatncct	1020
taaaaataat	mgattgatga	ttttctttat	ttccagagaa	tttattttat	aaatactttg	1080

60

tttacat	tttt	agattgt	tact	tgtcttt	tatt	taaatgat	ga	atctagt	ctg	aatcag	ctgt	1140
tattcc	agct	atcatg	ctta	agctatg	tca	acagcat	ttta	tttgtac	ttaa	tgcta	aatatt	1200
tccatc	aaaa	tttgcc	tgtg	gaatat	atac	agttct	ttaat	tttaa	actgt	cagttc	ttga	1260
gatata	accgt	gtgaag	ctat	tgtcag	cttc	tctat	tttcaa	aatgca	atca	gcatata	act	1320
atattg	atat	tagaag	atat	ttgttt	ttta	aaatat	atttg	atgtat	gata	aagatg	atct	1380
aatttg	tgaa	tgcatat	gtta	tgtgtg	gtta	cttttt	tataa	tgtgaa	ataa	tgaata	atga	1440
atttact	caa	aataaaa	acat	aggtta	atga	gaaaaaaaa	aaaaaaaa	aaaaaaaa	aaaa	aactc	gaa	1498

&lt;210&gt; 116

&lt;211&gt; 1797

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 116

ggaacac	aaaa	actgt	ggaaaa	agaa	atgaa	atctt	agcaga	agct	ggaact	ttttt	60	
atactt	tataa	aaatag	tatg	ttctt	atgtt	tctc	cttatg	catttt	atgtg	ttcact	ttaa	120
aatgtt	tttt	aatcta	aggt	tttct	ttgtt	tatgt	tcagg	taagga	actg	ttgtc	atgat	180
ctggaa	atgt	ttaaaa	acaat	gtttg	tttag	attct	gtgag	cagcaa	aaact	tatagt	gata	240
aaaatc	gatt	gttg	tttaata	tgatg	tttac	catgt	gcaca	tagta	atgaa	aagga	acata	300
aaagcc	cagc	aggct	cgtac	caaagt	caca	gcagta	aatgc	tatgt	actgc	agagt	ctgat	360
gagctg	gcct	ttgtg	cacac	ttttat	tttc	atggg	attgc	atctt	agctg	ttaaa	acttc	420
tagatt	gaaa	tttgac	agcc	agggt	tacat	attggg	gact	tttaa	agtgt	ctttc	caaag	480
agattt	catt	aaccg	tttag	attaga	atat	ctttcc	caat	tgttac	agtg	acata	tatgc	540
tgcaat	at	ttt	aactgga	gtatt	tagcca	catggg	ttat	ttttt	caatc	tgtgt	tttga	600
at	tttt	tttat	tgtgtgt	ttat	ttaaa	atatt	acata	tgcag	ctggg	gaga	ac	660
tgca	cataga	tttat	atatatt	aattt	gtaga	aaata	ttttc	tttat	atatatt	tcctt	accat	720
acaagg	tgcc	ttgtt	catca	ggaaa	acttt	tgttt	ttgtat	tttgac	aaaga	aaggc	acctt	780
cagagt	ttct	tttta	agtat	agttg	acaag	tgtata	aaatg	ttacac	tttac	tttcag	agtt	840
cttttt	tagat	ctaa	agaagt	cagtt	caaaa	atgg	aaatca	acaat	gttag	gagaa	atctg	900
aattct	gtta	agtt	tagtaag	tattat	gtat	agcat	ctgtt	ttta	accatt	tccatt	ctta	960
tccct	agtgt	atcag	ttgat	cacact	aaaga	aagct	ttaaag	attgag	catt	tgaa	ataaat	1020
gctct	ttata	aatg	attaga	ttttt	gaagg	gatatt	gaaa	tcatt	gcgct	gtgat	ttcat	1080
ctgtg	atgtg	aaaa	atcaat	ttatt	atcct	tggtg	ctttc	cccc	cacca	atgc	acaaat	1140
aattgt	gaac	agctt	gaaat	gactt	aaact	gtaat	ccaaa	tggg	acaatc	tgata	agaat	1200
ttcatg	catt	ggtag	ttaaa	taact	ttaa	tgct	aaagct	ttag	cttgaa	atttat	gttt	1260
agaaaa	acta	ttgat	ttccc	atgg	tatgaa	tata	actatt	gta	attcttc	aaatg	agact	1320
ctctc	acact	taaat	agtca	tata	ttaatt	aactt	atagg	aaata	agcat	actat	atgtt	1380
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agattt	caca	tgaat	gtaaa	tgtg	ttatat	ggag	acatgt	cttg	taaaaca	gttg	aatgta	1500
tgta	agtttt	ctgtt	ttgtga	aaatg	tagtt	aatg	tactca	ctgtg	ggaggt	cata	agggaag	1560
ctact	ttttt	tttaa	agtgg	aacct	aatta	aaat	attttc	aga	atcaaag	agact	ttaat	1620
ggta	aat	tttt	ttttc	ttat	ctctta	ctttt	tagtt	ttcaa	agtag	aaaa	aatcag	1680
gaatt	ttttt	atta	actagt	actt	acatat	taaa	ataaat	ttatt	atttg	ctaaaa	aaaaa	1740
aaaa	aaaaa	aaaa	aaaaa	aaaa	aaaaa	aact	agttct	agat	cgcggg	cggcc	gc	1797

&lt;210&gt; 117

&lt;211&gt; 952

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 117

ggcacg	agcc	tgccac	atag	aagg	tgcca	ttaat	tggat	gaac	gaatgg	gggag	ttaga	60
gtcagt	tacta	gaaaa	agcat	ggg	attatac	tttta	agagg	ccaa	atgaaa	attt	ggggaa	120
tagcc	at	ccag	gaat	ttt	aaaagg	agcc	at	tttt	ttaa	tgtc	aatat	180
ttatt	at	tttt	tttt	ttta	agcatt	attat	gggtg	ctt	attatag	gcat	ggtaaa	240
ccac	attatt	taa	atctcag	aat	ctatgag	ttt	gggtgaga	tc	actgcag	ttt	acagagg	300

41

aaaaaacagg	gcagagagaa	cggtaatctc	ctcaagttct	caactcttgc	acttaataga	360
tctagaattc	caaccagat	ctgatggtga	agtcagtata	agcttcctgg	agaaaggagt	420
agagttaagg	tgggggatgg	ggcttgaaga	cttgatagga	ttaggggttg	gagtgtcaac	480
tcggagatcc	acagtcaggc	ggaaggaacc	cacaaaggca	ggaatgcaca	cagcatgctc	540
agaggagatg	gaacctgaaa	atagagagaa	ttagcaagta	gtgcccattg	gatggagtaa	600
agagccatac	ctagaagggt	atcactgggt	aaccatgata	agagttttgg	cctgggtgctg	660
tggctcacgc	ctgtaatccc	agcactttgg	gaggccaagg	caggaggatc	acctgaggtc	720
aggagtccga	gaccagcctg	gccaacatga	tgaaccccca	tctgtactaa	aactacgaaa	780
attatctggg	tgtggcggca	ggcacctgta	atcccaccta	ctcggagggtg	acgcaggggg	840
aattgcttga	accggggagg	cagagggtgc	agtgaaccac	gatggtgcca	ctgcactcta	900
gcctgggcga	cagagcgaga	tccgtctcaa	aaaaaaaaaa	aaaaaactcg	ag	952

&lt;210&gt; 118

&lt;211&gt; 1185

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 118

ggcacgagct	tatgtctatg	ttttgagata	gaatccttct	attttatagc	agggatgggc	60
aaaccacaag	caaggggcca	aatccagcct	gctgcctgtt	tttgctaaaa	aagttttatt	120
ggaacacagc	catggccatt	cacttccata	tcattccaatg	gctgcttttg	tgctacaatt	180
gccaccatgc	ccagtggggc	ctgtggcaca	caactgcaga	agtgaagtgg	tgtggcagaa	240
atcacttagc	cttcaaagcc	taaagcactt	actatctgac	cctttccaga	aaaagtttgc	300
tgacctctgt	tttagagata	caaactaaca	tacttacaga	taagtgatct	gaatatgaag	360
caaattttca	acataatctg	ggttgatggg	gaaccgtgtt	acataataac	aaatccagag	420
ctaatacttg	ccaggtgagg	gctgtgcaga	cgatcacgac	actattctct	tttgcataatg	480
ttttccataa	taaaaagtct	tttgaaaaaa	tcaatgattt	aggggtttta	atatactgta	540
gtcacttttg	aaaacagttt	ggcagttcct	caaaaagttag	acatagaatt	accctatgac	600
ccagcagttc	cctttctaga	tataccccc	agagaattaa	aaacacacat	tcacacaaaa	660
acctgcacac	aatgtttcac	aggagcattg	ccttaatagc	aaaacaagcg	aaacaaccca	720
aatgcccac	aggtgacggg	tggataaaca	cagtgcggtc	tgtccataca	tggaaatgtga	780
ctcagccaca	ggcagkaatg	aagcgtgac	acacgcagca	acacggatga	accgtgaggt	840
cacggagtgg	agtgaagat	accagtcag	aagtcacaca	ccgtatgatg	ccattgacat	900
gaagtgttca	gagcaagtaa	atccttacag	atggaaggca	gagcgggtgac	tgccagggac	960
taggagtggg	gggccagggg	gtgactgcta	atgggtatgg	gatttcattt	cggggctgggt	1020
ggaaacgttc	cggagccaga	gagtagtgat	agctgcacaa	ctctatgtat	atgctatgaa	1080
tcaccaccga	atggtatatt	tttaaaggac	gaatttatgg	tatgtaaatt	gtgtctcaat	1140
aaagctgcta	tcttaaaatt	caaaaaaaaa	aaaaaaaaact	cgtag		1185

&lt;210&gt; 119

&lt;211&gt; 1098

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 119

tcgacccacg	cgcccgacga	actctagatc	tgggaataac	cctgtatcta	tttctttaca	60
tttttctttc	attaatgtat	ttatcactat	tttttttttg	tttttctttg	caggcctcag	120
ctgttgaaga	acgctctgca	gagagcagta	gagagggggc	agttagaaca	gataactggc	180
aaaggtgctt	cggggacatt	ccaggaactc	cgaccacct	ggtgcagagg	agtcttgtct	240
tgacctgctt	tgggagagtg	ttgtcttgat	gcttttctct	tcctccttgg	aaaacagctg	300
aagaaatcag	gggagaaacc	cctgcttggg	ggaagcctga	tggaaatagc	aatcttgtct	360
gccattgctg	ccatgaatga	gccgaagacc	tgctctacca	ctgctctgaa	gaagtatgtc	420
ctagagaatc	accaggaac	caattctaac	tatcaaagtc	atttgctgaa	aaaaaccctg	480
cagaaatgcg	aaaagaatgg	gtggatggaa	cagatctctg	ggaaaggggt	cagtggcacc	540
ttccagctct	gttttcccta	ttatcccagc	ccaggagttc	tgtttccgaa	gaaagagcca	600
gatgattcta	gagatgagga	tgaagatgaa	gatgagtcac	cagaagaaga	ctctgaggat	660

62

gaagagccgc	cacctaagag	aagggtgcag	aagaaaaccc	cagccaagtc	cccaggggaag	720
gccgcatctg	tgaagcagag	aggggtccaaa	cctgcaccta	aagtctcagc	tgcccagcgg	780
gggaaagcta	ggcccttgcc	taagaaagca	cctcctaagg	ccaaaacgcc	tgccaagaag	840
accagaccct	catccacagt	catcaagaaa	cctagtgggtg	gctcctcaaa	gaagcctgca	900
accagtgcga	gaaaggaagt	aaaattgccg	ggcaagggca	aatccaccat	gaagaagtct	960
ttcagagtga	aaaagtaaat	tttataggaa	aaaaggggtat	catgatgaaa	ttcaaaatct	1020
tattttctaa	gcacttttga	tatcaagcaa	gtggcttcct	ttttgagata	ttaaaaaaaa	1080
aaaaaaaaag	gcggccgc					1098

&lt;210&gt; 120

&lt;211&gt; 805

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 120

ggcacgaggt	ccctaattgt	cttgtaacct	gccctagggt	gaccagggca	ggggaatcat	60
ggcgagaagc	gtaagggcct	gatgaagaag	gtgtgctggg	tgtgggctct	agcccacttg	120
gttttgtgtg	agaggtggct	gacagcaggt	tgtttgctgt	atgtaggagt	tatccagccc	180
tgcaagggca	gtccctccag	tgtctgcaaa	gccgaagat	gtctgcatcc	aaaatacaga	240
ataaaaagat	atggttacta	caagtactca	gtaagactga	taatctgtca	tcatcatcct	300
catgccctta	aagcagagct	aactgatgat	taatatatgc	ttctatgtta	acagtcttgg	360
actttattaa	tgggtgggtg	aagttaactt	aatgtatgta	tgcaaaacta	aaagtggcat	420
ccttttctatt	aatgacccaa	ccattattca	agagctatgt	ctagttaggg	acttcagact	480
tttgaaagaa	atgaagaaat	aatgccagat	acatgggctc	gcacttggaa	tcccagctac	540
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ggattctgag	aagaaatatg	caaggtggaa	aagagcctag	aaagaaaggt	gacagatgct	720
gggatttggt	cgtcagaaga	gatattctagg	aaatagcatg	gcagccctca	agtactagct	780
ccacttaaaa	aaaaaaaaaa	aaaaa				805

&lt;210&gt; 121

&lt;211&gt; 1598

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1067)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1069)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1577)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 121

aggaaagaac	aaaggttatt	tcttgagaa	aagacaattt	attcaacacc	aacragggac	60
tcatcatatg	ggcacaactc	tgggtgcctt	ctatggagaa	aacctcaagt	aaagttttat	120
tctgcctttr	aaaaatgctt	caaaagtaga	ccctgtcccc	acacaggtca	agactacaga	180
gaaggctttg	tagaaatgtg	tcacctatgt	acacctgcta	cttacacatt	tccctcttttg	240
gaaaaatgag	atacttagaa	taacargaaa	attaagacat	actggcctgg	tgccagcaga	300

63

tggtttttct	atagacaaac	taggttagtg	tggaagatat	aggttaaaat	aaactatgct	360
gtttttattha	tcttcccaac	ctgattggca	gctagacttt	tttaggggtct	catttaaatgg	420
ccctgttttt	ttcattatta	tatttaaatga	tagggcagga	tttcgtatgc	aagctcttgt	480
ttctcaggct	gcctgcagaa	gaagtcgcta	taaattatct	gttggtctaca	tggtacaagg	540
cccattgact	catctgatgc	ttgttttgtt	aatttcttta	atatttttat	cacggggcag	600
tgggagggct	tgggctttta	gccacagctg	ttttaagact	tctgatctcc	tgccctgcag	660
gaataggtgg	gaagtcattg	aattttttaca	ctatagtaat	ttgcattccc	acataagttt	720
gagtgttacg	aaaacattcc	tttaaaggga	tctgtgctac	acaaaatatg	ccaggacctc	780
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gtaacggctc	tgctgccagg	gtttctctgg	gctcattctt	ccactgactt	aattatgate	1440
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atagcacata	ttgagatata	gttgtaactc	ctagtagata	ggaactgacc	ccaacaataa	1560
actttgataa	taaaganaaa	aaaaaaaaaa	actcgtag			1598

&lt;210&gt; 122

&lt;211&gt; 1020

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 122

cgncacgagg	tgaagttcaa	cccaatgcaa	ctttccttca	gtctttccgt	gaaagcgctt	60
gtgaaaaatg	aggtcatatt	tccctttctc	agtctgcccc	ttcccgtttt	gctctccggt	120
tttcttcttt	gtcttcacag	atgtttacct	atgttttttc	tttgtttttg	ctggttgaag	180
acatctaagt	gatccttttc	ccattctctt	tttactcat	aaatgtcctg	atgttttagca	240
aaaggcagtt	ctctttgcta	cttgagcttg	taaactgttg	ttaaatgagt	aacccaaaagg	300
aaagtccctg	cgaagttagt	taccattttca	gatacaagaa	ccgtttatct	tcccacgctg	360
acgaattttg	cgagtggagt	gattatthttt	ccttgtgttt	gtaattttatt	taagtaaatt	420
ccttgtttgt	ttttcttttc	agtacaccag	gggtatatat	tttcaatatg	acatgtacct	480
ttggttcagg	gctaagttag	agtctgaaaa	atgaagcctg	taggattcat	ggcagtgatc	540
taattgtgat	tcatcttact	gattgtaggg	caagaagagt	ggactaactc	aagacacaag	600
gcaccttcag	cgaggacagc	aaagggcgct	tacagagacc	agccatatgg	cagatactga	660
ttgtactgtc	tgatgttggt	aaatagccaa	tctccaccag	tcctgtatac	tgttcaaagt	720
aatttttttc	tatgaacaat	ccctttttta	ataaatcaaa	atgcttaaaa	tctgaatgga	780
tggaaactta	aactactttg	ttgaaacatc	aacctgggca	gaaaaaaaaa	aaaaaaagac	840
atgtaaaatt	ttgttatttc	cagtctgtat	atgaaaaaat	aggtcatcaa	aaggaaaaaa	900
aataactttg	attaactagt	gttaaacaaa	aaataggttt	actaaatctc	gtgccgaatt	960
cgatatcaag	cttatcgata	ccgtcgacct	cgtagggggg	gcccgtacct	aatcgctgt	1020

&lt;210&gt; 123

&lt;211&gt; 1378

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

64

&lt;400&gt; 123

atcttagcaa	tctccttggc	ccaaaacttc	accccatctt	ggaagggagg	ggagagagaa	60
tgttctgatc	tatatctgat	gagggcgtgt	ggttgggacc	tgagcatcct	cctgggtggg	120
ctagtgatgg	ggagagaggg	ctgttactca	cgactccctc	caacagaata	ccagaaacag	180
gcaggcagct	caggtgtatg	taaggatgtg	aggccaagaa	accagccctc	accaagttac	240
ccctgtaaat	ccttgtctcc	ccatgcacct	ctactttgag	tcagaaatgg	attcattgca	300
ggctcagttg	tttgtattat	gtgaatgaac	tgaacgtaac	caagcaccaa	gagagcccta	360
aagacacagt	agacctcctg	tagaagggtc	ctgatggacc	ttcaaacatt	gctyctccaa	420
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&lt;210&gt; 124

&lt;211&gt; 1146

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 124

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tataca						1146

&lt;210&gt; 125

&lt;211&gt; 1675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

65

&lt;400&gt; 125

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&lt;210&gt; 126

&lt;211&gt; 1064

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 126

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gtggatggga	cttacctgca	cgccccaggg	gtctttcagg	attcaggatg	acttttcttt	360
tacaatgggt	tcctctcggc	agagcccggg	ttgtggggga	tctgtgtggg	ttctcaacgc	420
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gaggatcgtg	catagcatag	gacgtctgaa	cctttgtaca	aatgtgtaga	tgacatcttg	960
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 <212> DNA  
 <213> Homo sapiens

66

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 taatatatat taaatacata gatagagtta tcataacaga gagaatctag taaaaaaaaa 180  
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 gcaaatggaa ttttctgatt aactgccata tattatatta tttgaataac tttagggraag 300  
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 <212> DNA  
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47

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 aaaaaaaggg cggccgc 1037

&lt;210&gt; 129

&lt;211&gt; 1146

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 129

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 aaaaaa 1146

&lt;210&gt; 130

&lt;211&gt; 1172

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 130

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68

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 <212> DNA  
 <213> Homo sapiens

<400> 131  
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 tttttttctg tattcatttt ttaatgagaa aagtttttaa tgtagtacag gttagacca 540  
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 ataaggcagt tgacttctta agtaaaagca atagtgtaaa atgtcatttt gtttggaatg 720  
 ttaagtgagc aaataaaaaa catgttgaaa ttgtaaaaaa aaaaaaaaaa aaaaaa 776

<210> 133  
 <211> 1543  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1055)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1143)  
 <223> n equals a,t,g, or c

&lt;400&gt; 133

69

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attgctgcaa	gcttatgctt	tcttgagta	tctgagagac	cgattaacaa	aacaagagtt	780
ccagaccctt	ttcttttttg	gtgtatcact	agctgcaggt	gctgtgttcc	ttagtgtcat	840
ctatttgact	tatacagggt	acattgcacc	atggagtggc	aggttttatt	cattgtggga	900
tactgggtat	gcaaaaatac	acattccaat	tattgcatca	gtgtctgagc	atcaacctac	960
gacttgggtg	tctttcttct	ttgatctaca	tattcttgta	tgtaccttcc	cagcaggcct	1020
ttggttctgc	atcaaaaata	tcaacgatga	aagantattt	ggtaagarag	gtttttaatg	1080
actactttga	tatggaatag	ttatttttct	ttttgagatt	atttacttta	aatttttggt	1140
tttctatggt	tgactctata	tattcaagat	aaattttctc	ctttattttg	cataggtgct	1200
taaccaagaa	aaattcactg	agaggctggg	catgggtggc	cacgcctkta	atcccagcac	1260
tttgggaggc	cgaggcgggc	ggatcacctg	aggtcaggag	ttcgagacca	gcctggccaa	1320
catggtgaaa	ccttgtctct	actaaaaata	caaaaattag	ccgaacatgg	tgggtgcatgc	1380
ctgtaatccc	agctactcag	gaggctgagg	caggataatt	gcttgaacct	gggaggcgga	1440
ggttgcagtg	agtcaagatc	aagccactgc	actccaccct	gggaatcaga	gcgggactct	1500
gtctcaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaagggcggc	cgc		1543

&lt;210&gt; 134

&lt;211&gt; 2157

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (309)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 134

caaaaaggac	cgcccatgga	agatgccatt	gcttcttccg	atgttcttga	gactgcttct	60
aaatctgcta	atccacccca	cacgattcaa	gcatcagaag	agcagagttc	aacccagca	120
ccggtgaaaa	agtctggcaa	gctgaggcag	caaatagatg	tgaaggcgga	actggagaag	180
cggcaaggag	ggaagcagct	actcaactta	gtggtcattg	gtcatgttga	tgctgggaaa	240
agtactctga	tgggccatat	gctttatctt	ctgggtaata	taaacaaaag	aactatgcat	300
aagtatganc	aggagtctaa	aaaggctggc	aaagcttcgt	ttgcatatgc	atgggtcttg	360
gatgaaactg	gcgaagaaa	ggaaagggga	gtaaccatgg	atgttggtat	gacaaagttt	420
gaaaccacaa	ccaaagttat	tacattaatg	gatgtccag	gccataagga	cttcattcca	480
aatatgatta	caggagcagc	ccaggcggat	gtagctgttt	tagttgtaga	tgccagcagg	540
ggagagtttg	aagctggatt	tgagactgga	ggacaaacac	gagagcatgg	actcttggtc	600
cgttctctgg	gagtgcagca	gcttgcaagt	gcagttaata	aaatggatca	ggttaattgg	660
caacaagaaa	ggtttcaaga	gattactgga	aaacttgggc	actttcttaa	gcaagcaggt	720
tttaaggaga	gtgatgtagg	ttttattcct	acaagtggtc	tcagtgggtga	aaatctaate	780
acaagatctc	agtcaagtga	actcacaata	tggtataaag	gactatgttt	attagaacaa	840
attgattcct	ttaagcctcc	ccagcgatct	attgacaaac	cttttagatt	atgtgtgtcc	900
gatgttttca	aagatcaagg	atctggattt	tgcataactg	gtaaaataga	agctgggttat	960
atccaaactg	gtgaccgact	actggcaatg	cctcctaattg	aaacttgtag	cgtgaaagga	1020
atcactctgc	atgatgaacc	tgctgactgg	gcggcagcag	gcgatcatgt	tagtcttact	1080

70

ttgggttgga	tggatatcat	caaaatcaat	gttggtgca	tattttgtgg	cccaaagta	1140
cccatataag	cttgactcgc	tttcagagcc	cgaatcctca	tctttaatat	tgaaattcct	1200
atcactaaag	gatttcctgt	gctgttacac	taccaaactg	tcagtgaacc	cgccgttatt	1260
aaacgattga	ttagtgtctt	aaacaaaagc	acgggtgaag	tcacaaagaa	aaagcctaag	1320
tttttgacta	aaggccagaa	tgcatgtgta	gagctacaga	cacaaagacc	aatagctctt	1380
gagctatata	aagactttta	agagctgggg	aggttcatgc	tacgttacgg	tggttctaca	1440
atagctgctg	gtgttggtcac	tgagataaaa	gaatgatggg	tcmgatttc	taccagttt	1500
ctggatacag	tgaaatagct	aacctctgty	tcaagaatgc	agttattaag	tcaaaggaac	1560
aatgtgcaat	tgatatgttt	ttagatgaga	gagaaaaatt	aaagctaaaa	ttagctgcaa	1620
agaagtatta	ataatcacct	ctgcaaaaat	tctaagttgc	caactggcaa	agraagtcta	1680
atgttaaaaa	caactttgcc	tttgaamcgt	taataaatgg	atttactttg	gtaagattta	1740
tggcaagtgt	caaaaatagt	atctgaagat	actgaatcat	catgaaatga	actctacttc	1800
tggccaaagc	acaatgtatt	tgcatgtttc	tcttttgatt	caattatact	gcacatgttt	1860
taaggaaaag	taacttaatt	gggtttttca	ggcagttgat	atttgacctt	agcttttttt	1920
tttttttttt	ttccagttta	tgctaagaaa	agatttgagg	aagggtataa	taaaagtatt	1980
ttgtggtgac	cataagaatg	tccctcccca	aacaagtata	cttgtgaaag	tttaatttgg	2040
aattagtggg	agctgttcct	ttgaaagcca	agatattatt	taagttgtta	agccagctaa	2100
taaaatgcct	tagtttgagc	ataaaaaaaaa	aaaaaaaaaaa	aaaaaaaaaaa	actcgag	2157

&lt;210&gt; 135

&lt;211&gt; 420

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 135

ggcacgagag	agagcagagc	tatacatagc	tatccaggtc	taacttcacg	aagaatagaa	60
tggtttcttt	tcatthttcaa	tgtacatcat	actttgtcag	actttttttt	cagttgcagc	120
tcttcgttgg	actggtgata	gtattggctt	tattaatctc	tcattctctc	acttattcat	180
tccacaaaca	tttgtagaag	gccaccaagc	tctagggaga	ggaaaatggg	tttataaatt	240
agtgtctttc	gggataaagg	aaattttata	tctgtactac	ttaatagtag	ccactagcca	300
catgtggttt	tcgaacaaga	tttccatcac	ctctccaacc	actttctcct	cattgggtcag	360
atctagaccc	cgagaaactg	ttcctttcat	tgttttctcc	gccttctaca	aactgagata	420

&lt;210&gt; 136

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 136

Met	Phe	Gln	Cys	Gly	Leu	Leu	Gln	Gln	Leu	Cys	Thr	Ile	Leu	Met	Ala
1				5					10					15	
Thr	Gly	Val	Pro	Ala	Asp	Ile	Leu	Thr	Glu	Thr	Ile	Asn	Thr	Val	Ser
			20					25					30		
Glu	Val	Ile	Arg	Gly	Cys	Gln	Val	Asn	Gln	Asp	Tyr	Phe	Ala	Ser	Val
		35				40						45			
Asn	Ala	Pro	Ser	Asn	Pro	Pro	Arg	Pro	Ala	Ile	Val	Val	Leu	Leu	Met
	50					55					60				
Ser	Met	Val	Asn	Glu	Arg	Gln	Pro	Phe	Val	Leu	Arg	Cys	Ala	Val	Leu
	65				70					75				80	
Tyr	Cys	Phe	Gln	Cys	Phe	Leu	Tyr	Lys	Asn	Gln	Lys	Gly	Gln	Gly	Glu
			85						90					95	

21

Ile Val Ser Thr Leu Leu Pro Ser Thr Ile Asp Ala Thr Gly Asn Ser  
 100 105 110  
 Val Ser Ala Gly Gln Leu Leu Cys Gly Gly Leu Phe Ser Thr Asp Ser  
 115 120 125  
 Leu Ser Asn Trp Cys Ala Ala Val Ala Leu Ala His Ala Leu Gln Glu  
 130 135 140  
 Asn Ala Thr Gln Lys Glu Gln Leu Leu Arg Val Gln Leu Ala Thr Ser  
 145 150 155 160  
 Ile Gly Asn Pro Pro Val Ser Leu Leu Gln Gln Cys Thr Asn Ile Leu  
 165 170 175  
 Ser Gln Gly Ser Lys Ile Gln Thr Arg Val Gly Leu Leu Met Leu Leu  
 180 185 190  
 Cys Thr Trp Leu Ser Asn Cys Pro Ile Ala Val Thr His Phe Leu His  
 195 200 205  
 Asn Ser Ala Asn Val Pro Phe Leu Thr Gly Gln Ile Ala Glu Asn Leu  
 210 215 220  
 Gly Glu Glu Glu Gln Leu Val Gln Gly Leu Cys Ala Leu Leu Leu Gly  
 225 230 235 240  
 Ile Ser Ile Tyr Phe Asn Asp Asn Ser Leu Glu Ser Tyr Met Lys Glu  
 245 250 255  
 Lys Leu Lys Gln Leu Ile Glu Lys Arg Ile Gly Lys Glu Asn Phe Ile  
 260 265 270  
 Glu Lys Leu Gly Phe Ile Ser Lys His Glu Leu Tyr Ser Arg Ala Ser  
 275 280 285  
 Gln Lys Pro Gln Pro Asn Phe Pro Ser Pro Glu Tyr Met Ile Phe Asp  
 290 295 300  
 His Glu Phe Thr Lys Leu Val Lys Glu Leu Glu Gly Val Ile Thr Lys  
 305 310 315 320  
 Ala Ile Tyr Lys Ser Ser Glu Glu Asp Lys Lys Lys Lys Lys  
 325 330

&lt;210&gt; 137

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 137

22

Met Thr Val Ala Ser Ile Arg His Ile Leu Val Glu Ile Trp Leu Pro  
 1 5 10 15  
 Ile Ala Leu Ala Met Gly Thr Arg Gly Leu Thr Gln Ile Val Ala Val  
 20 25 30  
 Ile Gln Ser Arg Ser Gln Trp Ala Leu Ser Xaa  
 35 40

&lt;210&gt; 138

&lt;211&gt; 87

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 138

Met Leu Phe Ile Phe Leu Leu Leu Ile Leu Ser Ile Thr Ala Ser Tyr  
 1 5 10 15  
 Ser Leu Thr Cys Ile Leu Ser Gly Ala Gly Glu Pro Ser Ser Val Ser  
 20 25 30  
 Ala Ser Val Val Ser Gly Pro Gly Phe Cys Leu Ala Ala Leu Leu Leu  
 35 40 45  
 Met Arg Thr Gly Gly Phe Ala Ala Thr Leu Leu Pro Val Ala Pro Thr  
 50 55 60  
 Glu Arg Phe Phe Ser Cys Cys Thr Val Leu Ser Ala Gln Arg Asn Val  
 65 70 75 80  
 Ser Arg Thr Arg Ser Pro Xaa  
 85

&lt;210&gt; 139

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (122)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 139

Met Leu Ser Thr Arg Trp Met Gly Leu His Leu Val Gln Ile Leu Trp  
 1 5 10 15  
 Arg Cys Trp Thr Ser Ser Ala Thr Ile Thr Ser Arg Lys Leu Ser Thr  
 20 25 30  
 Ala Leu Arg Ser Pro Val Leu Ser Gly Thr Gln Thr Ser Arg Ser Ser

35                      40                      73                      45

Gly Asp Ser Gly Trp Ser Met Lys Thr Ser Val Lys Ala Thr Pro His  
           50                                      55                                      60

Gln Met Ser Leu Arg Ser Gly Lys Glu Thr Pro Ser Ala Asp Ile Pro  
           65                                      70                                      75                                      80

Arg Ile His His Gln Leu Val Arg Leu Arg His Gln Ala His Gly Gly  
                                   85                                      90                                      95

Trp Ser Pro His Gly Val Pro Glu Gln Gly Thr Met Pro Leu Val Leu  
                           100                                      105                                      110

Pro Pro Val Ser Cys Asp Ile Gln Pro Xaa  
           115                                      120

&lt;210&gt; 140

&lt;211&gt; 276

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (131)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (276)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 140

Met Ala Asn Thr Gly Val Phe Gly Phe Ser Phe Leu Leu Leu Thr Val  
           1                                      5                                      10                                      15

Ala Leu Leu Ala Ser Tyr Ser Val His Leu Leu Leu Ser Met Cys Ile  
                           20                                      25                                      30

Gln Thr Ala Val Thr Ser Tyr Glu Asp Leu Gly Leu Phe Ala Phe Gly  
           35                                      40                                      45

Leu Pro Gly Lys Leu Val Val Ala Gly Thr Ile Ile Ile Gln Asn Ile  
           50                                      55                                      60

Gly Ala Met Ser Ser Tyr Leu Leu Ile Ile Lys Thr Glu Leu Pro Ala  
           65                                      70                                      75                                      80

Ala Ile Ala Glu Phe Leu Thr Gly Asp Tyr Ser Arg Tyr Trp Tyr Leu  
                           85                                      90                                      95

Asp Gly Gln Thr Leu Leu Ile Ile Ile Cys Val Gly Ile Val Phe Pro  
           100                                      105                                      110

Leu Ala Leu Leu Pro Lys Ile Gly Phe Leu Gly Tyr Thr Ser Ser Leu  
           115                                      120                                      125

24

Ser	Phe	Xaa	Phe	Met	Met	Phe	Phe	Ala	Leu	Val	Val	Ile	Ile	Lys	Lys
130						135					140				
Trp	Ser	Ile	Pro	Cys	Pro	Leu	Thr	Leu	Asn	Tyr	Val	Glu	Lys	Gly	Phe
145					150					155					160
Gln	Ile	Ser	Asn	Val	Thr	Asp	Asp	Cys	Lys	Pro	Lys	Leu	Phe	His	Phe
				165					170					175	
Ser	Lys	Glu	Ser	Ala	Tyr	Ala	Leu	Pro	Thr	Met	Ala	Phe	Ser	Phe	Leu
			180					185					190		
Cys	His	Thr	Ser	Ile	Leu	Pro	Ile	Tyr	Cys	Glu	Leu	Gln	Ser	Pro	Ser
		195					200					205			
Lys	Lys	Arg	Met	Gln	Asn	Val	Thr	Asn	Thr	Ala	Ile	Ala	Leu	Ser	Phe
						210		215				220			
Leu	Ile	Tyr	Phe	Ile	Ser	Ala	Leu	Phe	Gly	Tyr	Leu	Thr	Phe	Tyr	Gly
225					230					235					240
Ser	His	Ser	Val	Ala	Gln	Val	Gly	Val	Gln	Trp	Cys	Asp	Leu	Ser	Ser
				245					250					255	
Leu	Gln	Pro	Leu	Pro	Pro	Gly	Leu	Lys	Gln	Ser	Ser	His	Leu	Ser	Leu
			260					265					270		
Gln	Ser	Ser	Xaa												
			275												

&lt;210&gt; 141

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (138)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (195)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 141

Met	Lys	Leu	Ala	Ser	Gly	Phe	Leu	Val	Leu	Trp	Leu	Ser	Leu	Gly	Gly
1				5					10					15	

Gly	Leu	Ala	Gln	Ser	Asp	Thr	Ser	Pro	Asp	Thr	Glu	Glu	Ser	Tyr	Ser
			20					25					30		

Asp	Trp	Gly	Leu	Arg	His	Leu	Arg	Gly	Ser	Phe	Glu	Ser	Val	Asn	Ser
		35					40					45			

Tyr	Phe	Asp	Ser	Phe	Leu	Glu	Leu	Leu	Gly	Gly	Lys	Asn	Gly	Val	Cys
		50					55				60				

Gln Tyr Arg Cys Arg Tyr Gly Lys Ala Pro Met Pro Arg Pro Gly Tyr  
 65 70 75 80

Lys Pro Gln Glu Pro Asn Gly Cys Gly Ser Tyr Phe Leu Gly Leu Lys  
 85 90 95

Val Pro Glu Ser Met Asp Leu Gly Ile Pro Ala Met Thr Lys Cys Cys  
 100 105 110

Asn Gln Leu Asp Val Cys Tyr Asp Thr Cys Gly Ala Asn Lys Tyr Arg  
 115 120 125

Cys Asp Ala Lys Phe Arg Trp Cys Leu Xaa Ser Ile Cys Ser Asp Leu  
 130 135 140

Lys Arg Ser Leu Gly Phe Val Ser Lys Val Glu Ala Cys Asp Ser Leu  
 145 150 155 160

Val Asp Thr Val Phe Asn Thr Val Trp Thr Leu Gly Cys Arg Pro Phe  
 165 170 175

Met Asn Ser Gln Arg Ala Ala Cys Ile Cys Ala Glu Glu Glu Lys Glu  
 180 185 190

Glu Leu Xaa  
 195

&lt;210&gt; 142

&lt;211&gt; 183

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (183)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 142

Met Leu Leu Leu Cys His Ala Leu Ala Ile Ala Val Val Gln Ile Val  
 1 5 10 15

Ile Phe Ser Glu Ser Trp Ala Phe Ala Lys Asn Ile Asn Phe Tyr Asn  
 20 25 30

Val Arg Pro Pro Leu Asp Pro Thr Pro Phe Pro Asn Ser Phe Lys Cys  
 35 40 45

Phe Thr Cys Glu Asn Ala Gly Asp Asn Tyr Asn Cys Asn Arg Trp Ala  
 50 55 60

Glu Asp Lys Trp Cys Pro Gln Asn Thr Gln Tyr Cys Leu Thr Val His  
 65 70 75 80

His Phe Thr Ser His Gly Arg Ser Thr Ser Ile Thr Lys Lys Cys Ala  
 85 90 95

76

Ser Arg Ser Glu Cys His Phe Val Gly Cys His His Ser Arg Asp Ser  
                   100                                  105                                  110

Glu His Thr Glu Cys Arg Ser Cys Cys Glu Gly Met Ile Cys Asn Val  
                   115                                  120                                  125

Glu Leu Pro Thr Asn His Thr Asn Ala Val Phe Ala Val Met His Ala  
                   130                                  135                                  140

Gln Arg Thr Ser Gly Ser Ser Ala Pro Thr Leu Tyr Leu Thr Ser Ala  
                   145                                  150                                  155                                  160

Cys Leu Gly Leu Cys Ala Ser Ile Ala Val Met Pro Pro Phe Leu Gly  
                                   165                                  170                                  175

Glu Ala Glu Thr Ser Leu Xaa  
                                   180

<210> 143  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (122)  
 <223> Xaa equals stop translation

<400> 143  
 Met Leu Arg Gly Thr Met Thr Ala Trp Arg Gly Met Arg Pro Glu Val  
   1                                  5                                  10                                  15

Thr Leu Ala Cys Leu Leu Leu Ala Thr Ala Gly Cys Phe Ala Asp Leu  
                   20                                  25                                  30

Asn Glu Val Pro Gln Val Thr Val Gln Pro Ala Ser Thr Val Gln Lys  
                   35                                  40                                  45

Pro Gly Gly Thr Val Ile Leu Gly Cys Val Val Glu Pro Pro Arg Met  
                   50                                  55                                  60

Asn Val Thr Trp Arg Leu Asn Gly Lys Glu Leu Asn Gly Ser Asp Asp  
                   65                                  70                                  75                                  80

Ala Leu Gly Val Leu Ile Thr His Gly Thr Leu Val Ile Thr Ala Leu  
                                   85                                  90                                  95

Asn Asn His Thr Val Gly Arg Tyr Gln Cys Val Ala Arg Met Pro Ala  
                   100                                  105                                  110

Gly Ala Val Ala Thr Cys Gln Pro Leu Xaa  
                   115                                  120

<210> 144  
 <211> 267  
 <212> PRT

&lt;213&gt; Homo sapiens

??

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (267)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 144

Met	Trp	Trp	Phe	Gln	Gln	Gly	Leu	Ser	Phe	Leu	Pro	Ser	Ala	Leu	Val
1				5					10					15	

Ile	Trp	Thr	Ser	Ala	Ala	Phe	Ile	Phe	Ser	Tyr	Ile	Thr	Ala	Val	Thr
			20					25					30		

Leu	His	His	Ile	Asp	Pro	Ala	Leu	Pro	Tyr	Ile	Ser	Asp	Thr	Gly	Thr
	35						40					45			

Val	Ala	Pro	Glu	Lys	Cys	Leu	Phe	Gly	Ala	Met	Leu	Asn	Ile	Ala	Ala
	50					55					60				

Val	Leu	Cys	Ile	Ala	Thr	Ile	Tyr	Val	Arg	Tyr	Lys	Gln	Val	His	Ala
65					70					75					80

Leu	Ser	Pro	Glu	Glu	Asn	Val	Ile	Ile	Lys	Leu	Asn	Lys	Ala	Gly	Leu
				85					90					95	

Val	Leu	Gly	Ile	Leu	Ser	Cys	Leu	Gly	Leu	Ser	Ile	Val	Ala	Asn	Phe
		100						105					110		

Gln	Lys	Thr	Thr	Leu	Phe	Ala	Ala	His	Val	Ser	Gly	Ala	Val	Leu	Thr
	115						120					125			

Phe	Gly	Met	Gly	Ser	Leu	Tyr	Met	Phe	Val	Gln	Thr	Ile	Leu	Ser	Tyr
	130					135					140				

Gln	Met	Gln	Pro	Lys	Ile	His	Gly	Lys	Gln	Val	Phe	Trp	Ile	Arg	Leu
145					150					155					160

Leu	Leu	Val	Ile	Trp	Cys	Gly	Val	Ser	Ala	Leu	Ser	Met	Leu	Thr	Cys
				165					170					175	

Ser	Ser	Val	Leu	His	Ser	Gly	Asn	Phe	Gly	Thr	Asp	Leu	Glu	Gln	Lys
		180						185					190		

Leu	His	Trp	Asn	Pro	Glu	Asp	Lys	Gly	Tyr	Val	Leu	His	Met	Ile	Thr
	195						200					205			

Thr	Ala	Ala	Glu	Trp	Ser	Met	Ser	Phe	Ser	Phe	Phe	Gly	Phe	Phe	Leu
	210					215					220				

Thr	Tyr	Ile	Arg	Asp	Phe	Gln	Lys	Ile	Ser	Leu	Arg	Val	Glu	Ala	Asn
225					230					235					240

Leu	His	Gly	Leu	Thr	Leu	Tyr	Asp	Thr	Ala	Pro	Cys	Pro	Ile	Asn	Asn
			245						250					255	

Glu	Arg	Thr	Arg	Leu	Leu	Ser	Arg	Asp	Ile	Xaa					
		260						265							

78

&lt;210&gt; 145

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 145

Met	Leu	Cys	His	Pro	His	Val	His	His	His	Leu	Val	Cys	Leu	Leu	Ala
1				5					10					15	

Thr	Leu	Thr	Phe	Ser	Leu	Asn	Ala	Ser	Cys	Ala	Glu	Gln	Thr	Phe	His
			20					25					30		

Ser	Gln	Gln	Ser	Asn	Gly	Glu	Phe	Met	Ala	Thr	Leu	Pro	Ser	Ile	Ser
		35					40					45			

Lys	Gln	Phe	Gly	Val	Ile	Val	Trp	Lys	Pro	Gln	Arg	Lys	Asp	Val	Ile
	50					55					60				

Arg	Leu	Pro	Val	Ala	Leu	Ser	Phe	Ser	Met	Gly	Leu	Gly	Leu	Leu	Ser
65					70					75					80

Pro	Ala	Leu	Gly	Arg	Phe	Leu	Ala	Ser	Glu	Leu	Xaa
			85						90		

&lt;210&gt; 146

&lt;211&gt; 109

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (109)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 146

Met	Ala	Ile	Leu	Leu	Ala	Cys	Phe	Thr	Ala	Val	Leu	Ala	Phe	Ile	Cys
1				5					10					15	

Leu	Gln	Phe	Trp	Cys	Val	Arg	Cys	His	Glu	Pro	Arg	Trp	Ser	Tyr	Arg
			20					25					30		

Ala	Gly	His	Met	Glu	Glu	Ala	Asn	Gly	Leu	Val	Arg	Trp	Pro	Glu	Glu
		35					40					45			

Ala	Pro	Asp	Leu	Gly	Gln	Arg	Glu	Glu	Asp	Leu	Gln	Gly	Leu	Pro	Leu
	50					55					60				

Val	Glu	Met	Pro	Arg	Lys	Asn	Ser	Arg	Asp	Gly	Ala	Glu	Leu	Asp	Pro
65					70					75					80

79

Glu Ala Asn Gln Asp Ala Pro Asp Ala Gly Ala Leu Gln Arg Gly Gly  
                                     85                                    90                                    95

Gly Asp Pro Pro Ala Ile Leu Pro His Cys Gly Glu Xaa  
                                     100                                    105

&lt;210&gt; 147

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (88)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 147

Met Leu Leu Arg Val Phe His Phe Phe Leu His Ile Leu His Lys Lys  
   1                                    5                                    10                                    15

Gln Thr Gly Val Ser Leu Leu Tyr Leu Leu Leu Thr Leu Phe Leu Leu  
                                     20                                    25                                    30

Gln Gln Gln Val Ile Pro Gln Pro Ser Leu Pro Leu Leu His Leu Val  
                                     35                                    40                                    45

Ser Phe Gln Ile Cys His Tyr Pro Phe Pro Gln Trp Met Leu Gln Tyr  
   50                                    55                                    60

Arg Gln Ala Lys Met Val Leu Gly Thr Arg Cys Gln Met Ser Leu Met  
   65                                    70                                    75                                    80

His Phe Gln Asn Ser Gln Asn Xaa  
                                     85

&lt;210&gt; 148

&lt;211&gt; 74

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (74)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 148

Met Ser Arg Val Val Ser Leu Phe Phe Phe Ile Leu Phe Ser Phe Phe  
   1                                    5                                    10                                    15

Phe Phe Ala Phe Ser Leu Ser Ser Ser Leu Ser Phe Val His Tyr Glu  
                                     20                                    25                                    30

Lys Leu Val Gln Val Lys Glu Cys Leu Asp Ser Phe Leu Lys Lys Ile  
                                     35                                    40                                    45

Lys Ile Lys Glu Tyr Lys Thr Arg Gln Cys Tyr His Leu Ile Arg Trp

50 55 80 60

Glu Asn Asn Gly Ala Lys Leu Gln Ser Xaa  
65 70

<210> 149  
<211> 72  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (72)  
<223> Xaa equals stop translation

<400> 149  
Met Ser Ala Ser Leu Lys Asn His Leu Thr His Cys Phe Leu Leu Leu  
1 5 10 15  
Leu Leu Lys Glu Leu Val Ser Pro Thr Met Ile Ser Phe Val Pro Thr  
20 25 30  
Leu Arg His Ser Tyr Arg Phe Phe Asn Leu Phe Ser Cys Asp Ala Glu  
35 40 45  
Ser Thr Lys Glu Ser Pro Gly Arg Thr Val Gln Phe Ser Lys Thr Pro  
50 55 60  
Arg Gly Val Thr Met Phe Ile Xaa  
65 70

<210> 150  
<211> 152  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (152)  
<223> Xaa equals stop translation

<400> 150  
Met Lys Tyr Gly Leu Thr Gly Pro Trp Ile Lys Arg Leu Leu Pro Val  
1 5 10 15  
Ile Phe Leu Val Gln Ala Ser Gly Met Asn Val Tyr Met Ser Arg Ser  
20 25 30  
Leu Glu Ser Ile Lys Gly Ile Ala Val Met Asp Lys Glu Gly Asn Val  
35 40 45  
Leu Gly His Ser Arg Ile Ala Gly Thr Lys Ala Val Arg Glu Thr Leu  
50 55 60  
Ala Ser Arg Ile Val Leu Phe Gly Thr Ser Ala Leu Ile Pro Glu Val  
65 70 75 80

81

Phe Thr Tyr Phe Phe Lys Arg Thr Gln Tyr Phe Arg Lys Asn Pro Gly  
                             85                            90                            95

Ser Leu Trp Ile Leu Lys Leu Ser Cys Thr Val Leu Ala Met Gly Leu  
                             100                            105                            110

Met Val Pro Phe Ser Phe Ser Ile Phe Pro Gln Ile Gly Gln Ile Gln  
                             115                            120                            125

Tyr Cys Ser Leu Glu Glu Lys Ile Gln Ser Pro Thr Glu Glu Thr Glu  
                             130                            135                            140

Ile Phe Tyr His Arg Gly Val Xaa  
 145                            150

<210> 151  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals stop translation

<400> 151  
 Met Leu Arg Val Ala Gly Val Leu Gln Phe Leu Pro Leu Ser Tyr Gly  
   1                            5                            10                            15

Thr Lys Val Ala Ser Leu Trp Asn Thr Tyr Glu Asn Val Val Met Pro  
                             20                            25                            30

Pro Ser Phe Thr Thr Thr Leu Val Leu Pro Leu Leu Ser His Glu Phe  
                             35                            40                            45

Tyr Asn Tyr Ser Tyr Pro Phe Ala Cys Asp Gln Lys Xaa  
                             50                            55                            60

<210> 152  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (89)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (91)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

<222> (94)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (97)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (98)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (123)  
 <223> Xaa equals stop translation  
  
 <400> 152  
 Met His Arg Ser Glu Pro Phe Leu Lys Met Ser Leu Leu Ile Leu Leu  
 1 5 10 15  
 Phe Leu Gly Leu Ala Glu Ala Cys Thr Pro Arg Glu Val Asn Leu Leu  
 20 25 30  
 Lys Gly Ile Ile Gly Leu Met Ser Arg Leu Ser Pro Asp Glu Ile Leu  
 35 40 45  
 Gly Leu Leu Ser Leu Gln Val Leu His Glu Glu Thr Ser Gly Cys Lys  
 50 55 60  
 Glu Glu Val Lys Pro Phe Ser Gly Thr Thr Pro Ser Arg Lys Pro Leu  
 65 70 75 80  
 Pro Lys Arg Glu Glu His Val Glu Xaa Pro Xaa Asn Ala Xaa Thr Trp  
 85 90 95  
 Xaa Xaa Thr Tyr Leu Phe Val Ser Tyr Asn Lys Gly Asp Trp Phe Thr  
 100 105 110  
 Phe Ser Ser Gln Val Leu Leu Pro Leu Leu Xaa  
 115 120

<210> 153  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (55)  
 <223> Xaa equals stop translation

<400> 153  
 Met Ser Pro Cys Ala His Ile Cys Leu Tyr Val Leu Val Phe Leu Cys  
 1 5 10 15

93

Asn Val Thr Arg Cys Lys Cys Val Arg Ala Phe Thr Thr Trp Asp Thr  
                   20                                  25                                  30

Glu Lys Val Lys Tyr Phe Met Ala His Trp Ser Lys Leu Lys Arg Val  
                   35                                  40                                  45

Arg Gly Thr Arg Val Glu Xaa  
                   50                                  55

&lt;210&gt; 154

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (93)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (111)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 154

Met Phe Leu Ala Ser Trp Leu Leu Phe Cys Ile Val Ala Pro Lys Asp  
   1                                  5                                  10                                  15

Asp Ala His Leu Ser Phe Ile Gln Cys Lys Asp Ile Trp Lys Asp Asn  
                   20                                  25                                  30

Arg Lys Tyr Ser Cys Phe His Phe Lys Ser Asp Gln Leu Leu Glu Leu  
                   35                                  40                                  45

Ala Ser Lys Ala Cys Thr Ser Phe Gln Ala Gln Ser Arg Ser Phe Thr  
                   50                                  55                                  60

Ala Gly Ala Val Pro Ser Glu His Pro Glu Leu Pro Cys Gly Ser Gln  
   65                                  70                                  75                                  80

Gln Leu Cys Cys Gly Cys Thr Ala Arg Leu Gly Gly Xaa Trp Ile Gly  
                                   85                                  90                                  95

Ala Ser Arg Cys Gly Ser Gly Ser Ala Phe Leu Ala Ser Pro Xaa  
                   100                                  105                                  110

&lt;210&gt; 155

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 155

Met Ser Leu Gln Ala Ile Asp Leu Leu Trp Ser Leu Cys Thr Gln Thr  
 1 5 10 15

Ser Leu Leu Thr Leu Ile Cys Ile Cys Ser His Ser Gln Ala Leu Ser  
 20 25 30

Ser Ser Pro Gln Leu His Leu Arg Ser Ser Ser Ile Arg Phe Ser Xaa  
 35 40 45

&lt;210&gt; 156

&lt;211&gt; 82

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 156

Met Phe His Phe Gly Leu Trp Asp Leu His Phe Phe Leu Ile Val Met  
 1 5 10 15

Ala His Arg Asp Asp Cys Ser Phe Lys Gly Gly Cys Gly Leu Leu Glu  
 20 25 30

Arg Phe Gln Cys Pro His Thr Ser Phe Ser Ser Ala Ser Gln Lys Arg  
 35 40 45

Leu Ala Asp Gly Met Glu Cys Leu Cys Glu Ile Glu Arg Thr Gln Thr  
 50 55 60

Arg Ile Arg Lys Ile Cys Leu Pro Thr Leu His Gly His Leu Leu Ala  
 65 70 75 80

Val Xaa

&lt;210&gt; 157

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (108)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (113)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

85

&lt;221&gt; SITE

&lt;222&gt; (156)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 157

Met	Met	Ala	Arg	Gln	Thr	Gly	Val	Phe	Tyr	Leu	Thr	Leu	Val	Leu	Ile
1				5					10					15	
Leu	Val	Thr	Ser	Gly	Leu	Phe	Phe	Ala	Phe	Asp	Cys	Pro	Tyr	Leu	Ala
			20					25					30		
Val	Lys	Ile	Thr	Pro	Ala	Ile	Pro	Ala	Val	Ala	Gly	Ile	Leu	Phe	Phe
		35					40					45			
Phe	Val	Met	Gly	Thr	Leu	Leu	Arg	Thr	Ser	Phe	Ser	Asp	Pro	Gly	Val
		50				55						60			
Leu	Pro	Arg	Ala	Thr	Pro	Asp	Glu	Ala	Ala	Asp	Leu	Glu	Arg	Gln	Ile
	65					70				75					80
Gly	Asn	Thr	Glu	Ser	Leu	Pro	Met	Ala	Ser	Gly	His	Phe	Pro	Pro	Gly
				85					90					95	
Pro	Ser	Tyr	Ser	Gly	Glu	Gly	Arg	Pro	Arg	Ala	Xaa	Gln	Glu	Glu	Leu
			100					105					110		
Xaa	Ala	Gly	Lys	Glu	Gly	Gly	Gln	Lys	Ser	Ala	Phe	Leu	Ser	Ser	Leu
		115					120					125			
Gly	Gly	Gln	Asp	Glu	Leu	Lys	Lys	Arg	Cys	Asp	Ile	Arg	Leu	Glu	Gly
	130						135				140				
Gln	Val	Ser	Trp	Arg	Gln	Asp	Cys	Arg	Pro	Thr	Xaa				
145						150				155					

&lt;210&gt; 158

&lt;211&gt; 295

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (295)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 158

Met	Arg	Leu	Asp	Lys	Pro	Ile	Gly	Thr	Trp	Leu	Leu	Tyr	Leu	Pro	Cys
1				5					10					15	
Thr	Trp	Ser	Ile	Gly	Leu	Ala	Ala	Glu	Pro	Gly	Cys	Phe	Pro	Asp	Trp
			20					25					30		
Tyr	Met	Leu	Ser	Leu	Phe	Gly	Thr	Gly	Ala	Ile	Leu	Met	Arg	Gly	Ala
		35					40					45			

86

Gly	Cys	Thr	Ile	Asn	Asp	Met	Trp	Asp	Gln	Asp	Tyr	Asp	Lys	Lys	Val
50						55					60				
Thr	Arg	Thr	Ala	Asn	Arg	Pro	Ile	Ala	Ala	Gly	Asp	Ile	Ser	Thr	Phe
65					70					75					80
Gln	Ser	Phe	Val	Phe	Leu	Gly	Gly	Gln	Leu	Thr	Leu	Ala	Leu	Gly	Val
				85					90					95	
Leu	Leu	Cys	Leu	Asn	Tyr	Tyr	Ser	Ile	Ala	Leu	Gly	Ala	Gly	Ser	Leu
			100					105					110		
Leu	Leu	Val	Ile	Thr	Tyr	Pro	Leu	Met	Lys	Arg	Ile	Ser	Tyr	Trp	Pro
		115					120						125		
Gln	Leu	Ala	Leu	Gly	Leu	Thr	Phe	Asn	Trp	Gly	Ala	Leu	Leu	Gly	Trp
	130					135					140				
Ser	Ala	Ile	Lys	Gly	Ser	Cys	Asp	Pro	Ser	Val	Cys	Leu	Pro	Leu	Tyr
145					150					155					160
Phe	Ser	Gly	Val	Met	Trp	Thr	Leu	Ile	Tyr	Asp	Thr	Ile	Tyr	Ala	His
				165					170					175	
Gln	Asp	Lys	Arg	Asp	Asp	Val	Leu	Ile	Gly	Leu	Lys	Ser	Thr	Ala	Leu
			180					185						190	
Arg	Phe	Gly	Glu	Asn	Thr	Lys	Pro	Trp	Leu	Ser	Gly	Phe	Ser	Val	Ala
		195					200					205			
Met	Leu	Gly	Ala	Leu	Ser	Leu	Val	Gly	Val	Asn	Ser	Gly	Gln	Thr	Ala
	210					215					220				
Pro	Tyr	Tyr	Ala	Ala	Leu	Gly	Ala	Val	Gly	Ala	His	Leu	Thr	His	Gln
225					230				235						240
Ile	Tyr	Thr	Leu	Asp	Ile	His	Arg	Pro	Glu	Asp	Cys	Trp	Asn	Lys	Phe
				245					250					255	
Ile	Ser	Asn	Arg	Thr	Leu	Gly	Leu	Ile	Val	Phe	Leu	Gly	Ile	Val	Leu
			260					265					270		
Gly	Asn	Leu	Trp	Lys	Glu	Lys	Lys	Thr	Asp	Lys	Thr	Lys	Lys	Gly	Ile
		275					280					285			
Glu	Asn	Lys	Ile	Glu	Asn	Xaa									
	290					295									

&lt;210&gt; 159

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (60)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 159

87

Met Gly Pro Phe Leu Leu Val Phe Leu Phe Pro Ile Leu Arg Val Cys  
 1 5 10 15

Gly Ile Ile Arg Glu Pro Thr Gln Asp Trp Ser Val Leu Leu Glu Arg  
 20 25 30

Ala Arg Leu Thr Ala Pro Gly Gln Pro Pro Ala Leu Phe Pro Leu Glu  
 35 40 45

Ser Gly Pro Met Ala Thr Ala Gln Asn Thr Ser Xaa  
 50 55 60

&lt;210&gt; 160

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (32)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (101)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (115)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (122)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 160

Met Cys Ser His Ser Thr Leu Ile His Leu Tyr Leu Val Leu Pro Phe  
 1 5 10 15

Phe Phe Leu Phe Leu Pro Ser Ser Phe Pro Phe Pro Ser Xaa Ser Xaa  
 20 25 30

Ser Ser Ile Leu Pro Ser Leu Arg Leu Pro Pro Phe Phe Pro Pro Ser

35                                      40                      38                      45  
 Leu Phe Leu His Ser Ser Leu Pro Pro Ser Leu Ser His Pro Leu Gly  
     50                                      55                                      60  
 Leu Ser Ile Thr Ser Ser Arg Gln Ser Phe Leu Asp Tyr His His Leu  
     65                                      70                                      75                                      80  
 Cys Thr Lys His Leu Ser Xaa Thr Leu Cys Gly Leu Ile Tyr His Cys  
                                     85                                      90                                      95  
 Leu Asn Ile Phe Xaa Thr Arg Ala Val Met Trp His Met Gln Val Ser  
                                     100                                      105                                      110  
 Phe Leu Xaa Ile His Trp Leu Leu Pro Xaa  
                                     115                                      120

<210> 161  
 <211> 73  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (73)  
 <223> Xaa equals stop translation

<400> 161  
 Met Ser Ile Tyr His Val Cys Leu Ile Leu Leu Tyr Ile Thr Ser  
     1                                      5                                      10                                      15  
 His Ser His Gln Asn Met Ser Ser Cys Leu Gln Val Pro Leu Ser Leu  
                                     20                                      25                                      30  
 Leu Ser Cys Pro Leu Lys Gly Glu His Leu Ser Gln Phe Ala Gly Asp  
                                     35                                      40                                      45  
 His Ser Leu Pro Glu Val Arg Asp Arg Asn His His Cys Ile Leu Phe  
     50                                      55                                      60  
 Lys Glu Ser His Gln Lys Arg Lys Xaa  
     65                                      70

<210> 162  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (123)  
 <223> Xaa equals stop translation

<400> 162  
 Met Leu Ala Asn Phe Thr Leu Phe Ile Leu Thr Leu Ile Ser Phe Leu  
     1                                      5                                      10                                      15

89

Leu Leu Val Cys Ser Pro Cys Lys His Leu Lys Met Met Gln Leu His  
                   20                                  25                                  30  
 Gly Lys Gly Ser Gln Asp Leu Ser Thr Lys Val His Ile Lys Pro Leu  
                   35                                  40                                  45  
 Gln Thr Val Ile Ser Phe Leu Met Leu Phe Ala Ile Tyr Phe Leu Cys  
                   50                                  55                                  60  
 Ile Ile Thr Ser Thr Trp Asn Pro Arg Thr Gln Gln Ser Asn Leu Val  
                   65                                  70                                  75                                  80  
 Phe Leu Leu Tyr Gln Thr Leu Ala Ile Met Tyr Pro Ser Phe His Ser  
                                   85                                  90                                  95  
 Phe Ile Leu Ile Met Arg Ser Arg Lys Leu Lys Gln Thr Ser Leu Ser  
                                   100                                  105                                  110  
 Val Leu Cys Gln Val Thr Cys Trp Val Lys Xaa  
                   115                                  120

&lt;210&gt; 163

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (143)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 163

Met Pro Gly Pro Cys Leu Ser Gln Gln His Pro Phe Leu Ser Leu Ser  
   1                                  5                                  10                                  15  
 Leu Phe Pro Phe Cys Leu Trp Ile Cys Leu Ala Arg Val Pro Gly Val  
                   20                                  25                                  30  
 Arg Asn Ile Cys Lys Thr Gln Pro Ala Pro Ser Gln Pro Ser Leu Leu  
                   35                                  40                                  45  
 Gly Leu Gly Leu Ser His Pro Ala Ala Gly Thr Thr Asp Ala Gly Thr  
                   50                                  55                                  60  
 Gln Ser Leu Pro Arg Ser Gln His Lys Cys Thr Ser Ala Leu Trp Gly  
                   65                                  70                                  75                                  80  
 Leu Cys Pro Ala Gln Arg Pro Leu Leu Leu Pro Ala His Ile His Ser  
                                   85                                  90                                  95  
 Ser Gly His Gly Ala Pro Gln Glu Leu Gln Ser His Leu Ser His Arg  
                   100                                  105                                  110  
 Leu Pro Ala Ser Ala Ser Leu Ser Met Met Ser Pro Phe Ser Glu Ala  
                   115                                  120                                  125

90

Trp	Thr	His	Pro	Ser	Leu	Ser	Leu	Gly	Pro	Ala	Pro	Ser	His	Xaa
130							135					140		

&lt;210&gt; 164

&lt;211&gt; 117

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (117)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 164

Met	Pro	Gly	Gly	Thr	Arg	Cys	Arg	Val	Leu	Leu	Leu	Ser	Leu	Thr	Phe
1				5					10					15	

Gly	Thr	Ser	Met	Ala	Cys	Gly	Asn	Val	Gly	Leu	Arg	Leu	Cys	Pro	Trp
			20				25						30		

Thr	Trp	His	Asn	Trp	Leu	Leu	Pro	Pro	His	Leu	Cys	Ser	Xaa	Trp	Pro
		35					40					45			

Cys	Arg	Arg	Cys	Cys	Trp	Ala	Ala	Ala	Thr	Thr	His	Phe	Ser	Trp	Pro
50						55					60				

Pro	Trp	Val	Arg	Ser	Ala	Trp	Gly	Pro	Pro	Ala	Ala	Trp	Leu	Glu	Ser
65					70					75				80	

Ser	Gly	His	Pro	Leu	Pro	Ala	Val	Ala	Ser	Cys	Ser	Gln	Pro	Pro	Ala
				85					90					95	

Ser	Ala	Asp	Ser	Ser	Arg	Phe	Ser	Lys	Val	Pro	Cys	Cys	Arg	Arg	Arg
			100					105					110		

Gly	Trp	Thr	Arg	Xaa
				115

&lt;210&gt; 165

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (59)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 165

Met	Ser	Val	Cys	Leu	Pro	Leu	His	Leu	Pro	Phe	Leu	Met	Leu	Ala	Lys
1				5					10					15	

Val Ala Thr Ser Phe Cys Arg Trp Gln Leu<sup>9</sup> Thr Leu Phe Val Ser Thr  
                     20                    25                    30

Phe Tyr Lys Asp Ala Leu Val His Thr Val Asn Asp Arg Asn Gln Glu  
                     35                    40                    45

Ala Glu Leu Glu Ala Leu Lys Lys Ser Cys Xaa  
                     50                    55

<210> 166

<211> 126

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (126)

<223> Xaa equals stop translation

<400> 166

Met Lys Ala Leu Met Leu Leu Thr Leu Ser Val Leu Leu Cys Trp Val  
                     1                    5                    10                    15

Ser Ala Asp Ile Arg Cys His Ser Cys Tyr Lys Val Pro Val Leu Gly  
                     20                    25                    30

Cys Val Asp Arg Gln Ser Cys Arg Leu Glu Pro Gly Gln Gln Cys Leu  
                     35                    40                    45

Thr Thr His Ala Tyr Leu Gly Lys Met Trp Val Phe Ser Asn Leu Arg  
                     50                    55                    60

Cys Gly Thr Pro Glu Glu Pro Cys Gln Glu Ala Phe Asn Gln Thr Asn  
                     65                    70                    75                    80

Arg Lys Leu Gly Leu Thr Tyr Asn Thr Thr Cys Cys Asn Lys Asp Asn  
                     85                    90                    95

Cys Asn Ser Ala Gly Pro Arg Pro Thr Pro Ala Leu Gly Leu Val Phe  
                     100                    105                    110

Leu Thr Ser Leu Ala Gly Leu Gly Leu Trp Leu Leu His Xaa  
                     115                    120                    125

<210> 167

<211> 87

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (87)

<223> Xaa equals stop translation

<400> 167

12

Met Phe Leu Val Ala Val Trp Trp Arg Phe Gly Ile Leu Ser Ile Cys  
 1 5 10 15

Met Leu Cys Val Gly Leu Val Leu Gly Phe Leu Ile Ser Ser Val Thr  
 20 25 30

Phe Phe Thr Pro Leu Gly Asn Leu Lys Ile Phe His Asp Asp Gly Val  
 35 40 45

Phe Trp Val Thr Phe Ser Cys Ile Ala Ile Leu Ile Pro Val Val Phe  
 50 55 60

Met Gly Cys Leu Arg Ile Leu Asn Ile Leu Thr Cys Gly Ser His Trp  
 65 70 75 80

Ala Pro Ile Arg Trp Phe Xaa  
 85

&lt;210&gt; 168

&lt;211&gt; 63

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (63)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 168

Met Val Thr Gly Phe Phe Phe Ile Leu Met Thr Val Leu Trp Phe Xaa  
 1 5 10 15

Arg Glu Pro Gly Phe Val Pro Gly Trp Asp Ser Phe Phe Glu Lys Lys  
 20 25 30

Gly Tyr Arg Thr Asp Ala Thr Val Ser Val Phe Leu Gly Phe Leu Leu  
 35 40 45

Phe Leu Ile Pro Ala Xaa Glu Ala Leu Leu Trp Glu Lys Glu Xaa  
 50 55 60

&lt;210&gt; 169

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

93

&lt;222&gt; (48)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 169

Met	Ser	Gln	Leu	Cys	Phe	Ser	Leu	Leu	Leu	Ser	Ser	Thr	Cys	His	Gly
1				5					10					15	

Gly	Val	Ala	Ser	Leu	Leu	Thr	Ser	Asp	Leu	Ser	Ser	Gln	Ser	His	Arg
			20					25					30		

Phe	Ser	Ile	Cys	Thr	Asn	Val	Asn	His	Ser	Lys	Tyr	Ser	Ser	Leu	Xaa
		35					40					45			

&lt;210&gt; 170

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (84)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (137)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 170

Met	Leu	Phe	Ser	Leu	Arg	Glu	Leu	Val	Gln	Trp	Leu	Gly	Phe	Ala	Thr
1				5					10					15	

Phe	Glu	Ile	Phe	Val	His	Leu	Leu	Ala	Leu	Leu	Val	Phe	Ser	Val	Leu
			20					25					30		

Leu	Ala	Leu	Arg	Val	Asp	Gly	Leu	Val	Pro	Gly	Leu	Ser	Trp	Trp	Asn
		35					40					45			

Val	Phe	Val	Pro	Phe	Phe	Ala	Ala	Asp	Gly	Leu	Ser	Thr	Tyr	Phe	Thr
	50					55					60				

Thr	Ile	Val	Ser	Val	Arg	Leu	Phe	Gln	Asp	Gly	Glu	Lys	Arg	Leu	Ala
65					70					75					80

Val	Leu	Arg	Xaa	Phe	Trp	Val	Leu	Thr	Val	Leu	Ser	Leu	Lys	Phe	Val
			85					90						95	

Phe	Glu	Met	Leu	Leu	Cys	Gln	Lys	Leu	Ala	Glu	Gln	Thr	Arg	Glu	Leu
			100					105					110		

Trp	Phe	Gly	Leu	Ile	Thr	Ser	Pro	Leu	Phe	Ile	Leu	Leu	Gln	Leu	Leu
		115					120					125			

94

Met Ile Arg Ala Cys Arg Val Asn Xaa  
 130 135

&lt;210&gt; 171

&lt;211&gt; 89

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (40)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 171

Met Glu Leu Ser Phe Val Arg Arg Leu Leu Leu Phe Thr Phe Phe Phe  
 1 5 10 15

Ser Thr Phe Ser Pro Pro Pro Pro Thr Pro Cys Leu Glu Gly Leu Met  
 20 25 30

Ser Cys Leu Pro Ser Pro Leu Xaa Lys Asn Thr Ala Gly Ser Gln Thr  
 35 40 45

Lys Ser Leu Arg Glu Ile Gly Thr Gly Ile Ser Asp Thr His Val Ser  
 50 55 60

Pro Ser Pro Ala Gln Ala Pro Leu Cys Ser Arg Ser Pro Thr Trp Asp  
 65 70 75 80

Ser Ser Asp Pro Asn Ser Met Asp Xaa  
 85

&lt;210&gt; 172

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 172

Met Thr Met Val Met Glu Gln Val Tyr Leu Met Ser Phe Leu Leu Leu  
 1 5 10 15

Leu Leu Arg Thr Met Met Lys Ala His Trp Thr Tyr Thr Leu Gly Trp  
 20 25 30

Thr Val Leu Phe Leu Thr Ala Leu Pro Asn Pro Val Tyr His Gln Glu

35

40

95

45

Ile Val Trp Thr Tyr Met Lys Arg Ser Xaa  
50 55

&lt;210&gt; 173

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 173

Met Asp Thr Asp Asn Gly Gly Arg His Phe Lys Pro Phe Lys Leu Val  
1 5 10 15

Leu Phe Val Val Leu Leu Ile Lys Ile Leu Leu Ile Leu Ala Lys Thr  
20 25 30

Asn Cys Cys Asp Lys Leu Val Phe Phe Gly Cys Phe Lys His Thr Leu  
35 40 45

Thr Asn Phe Leu Ile Pro Leu Leu Val Pro Pro Ile Val Leu Lys Xaa  
50 55 60

&lt;210&gt; 174

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (61)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 174

Met Cys Leu Trp Gly Gln Ala Asn Leu Gly Leu Ile Leu Phe Gln His  
1 5 10 15

Cys Leu Thr Lys Phe Met Gly Gly Tyr Cys Phe Gly Leu Gly Ser Cys  
20 25 30

Thr Arg Pro Leu Arg Asp Gln Thr Lys Met Glu Ser Leu Ile Leu Lys  
35 40 45

Leu Gln Val Thr Glu Pro Lys Leu Ser Cys Phe Ile Xaa  
50 55 60

&lt;210&gt; 175

96

<211> 104  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (104)  
 <223> Xaa equals stop translation

<400> 175

Met	Gly	Met	Ala	Gly	Ala	Leu	Ser	Ile	Leu	Leu	Phe	Ser	Leu	Pro	Ser
1				5					10					15	
His	Gly	Trp	Pro	Ser	Pro	Pro	Lys	Pro	Pro	Phe	Pro	Cys	Cys	Gln	Pro
			20				25						30		
Leu	Cys	His	Ser	Leu	Ile	Leu	Gly	Arg	Arg	Lys	Gly	Arg	Phe	Glu	Gly
		35					40					45			
Glu	Gly	Glu	Lys	Ala	Tyr	Gly	Trp	Val	Trp	Phe	Leu	Pro	Phe	Pro	Glu
	50					55					60				
Gly	Leu	Thr	Val	Pro	Gly	Trp	Pro	Gln	Gly	Arg	Gln	Gly	Pro	His	Tyr
65					70					75					80
Ala	Cys	Ala	Leu	Val	Lys	Val	Thr	Pro	Ala	Ile	Tyr	Gln	Gln	Pro	Trp
				85					90					95	
His	Val	Pro	Ala	Pro	Gln	Glu	Xaa								
					100										

<210> 176  
 <211> 293  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (293)  
 <223> Xaa equals stop translation

<400> 176

Met	Leu	Arg	Val	Leu	Cys	Leu	Leu	Arg	Pro	Trp	Arg	Pro	Leu	Arg	Ala
1				5					10					15	
Arg	Gly	Cys	Ala	Ser	Asp	Gly	Ala	Ala	Gly	Gly	Ser	Glu	Ile	Gln	Val
			20					25					30		
Arg	Ala	Leu	Ala	Gly	Pro	Asp	Gln	Gly	Ile	Thr	Glu	Ile	Leu	Met	Asn
		35					40					45			
Arg	Pro	Ser	Ala	Arg	Asn	Ala	Leu	Gly	Asn	Val	Phe	Val	Ser	Glu	Leu
	50					55					60				
Leu	Glu	Thr	Leu	Ala	Gln	Leu	Arg	Glu	Asp	Arg	Gln	Val	Arg	Val	Leu
65					70					75					80

Gly Glu Leu His Pro Pro Val Ala Ala Thr Cys Leu Leu Thr Val Leu

20

25

30

Leu Gly Cys Leu Ile Gly Val Ser Ser Asp Gly Trp Ile Xaa  
 35 40 45

&lt;210&gt; 178

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 178

Met Cys Ile Pro Glu Ala Leu Gly Lys Asn Ser Leu Phe Leu Ser Ser  
 1 5 10 15

Thr Phe Leu Trp Leu Leu Ala Phe Phe Gly Leu Trp Ser His His Ser  
 20 25 30

Tyr Leu Glu Gly Gln His Leu Gln Ile Cys Phe Phe Phe Thr Xaa  
 35 40 45

&lt;210&gt; 179

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 179

Met Thr Thr Ser Leu Phe Gly Leu Val Cys Val Val Cys Gln Gly Ala  
 1 5 10 15

Gly Val Ser Ala Phe Thr Gln Val Asn Leu Phe Ser Phe Ser Leu Val  
 20 25 30

Ile Val Lys Lys Gln Asn Lys Thr Ser Cys Glu Pro Phe Gly Thr Ser  
 35 40 45

Gly Lys Val Pro Leu Leu Xaa  
 50 55

&lt;210&gt; 180

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

99

&lt;222&gt; (67)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 180

Met	Leu	Ile	Tyr	Trp	Leu	Gln	Ser	Ser	Phe	Ile	Leu	Ser	Ala	Phe	Val
1					5				10					15	

Leu	Ile	Asn	Ser	Pro	Val	Thr	Thr	Gly	Ile	Gln	Lys	Ser	Cys	Cys	Lys
			20					25					30		

Phe	Phe	Pro	Val	Ser	Ile	Asn	Leu	Cys	Phe	Ala	Ser	Leu	His	Arg	Met
		35					40					45			

Lys	Val	Val	Thr	Leu	Val	Ala	Leu	Gln	Trp	Leu	Asn	Ile	Ala	Leu	Arg
	50					55					60				

Ser	Ser	Xaa
65		

&lt;210&gt; 181

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 181

Met	Val	Cys	Cys	Gly	Phe	Phe	Leu	Leu	Trp	Ser	Arg	Val	Arg	Ser	Tyr
1				5					10					15	

Met	Lys	Leu	Ser	Gly	His	Arg	Trp	Ser	Ser	Ser	Cys	Pro	His	His	Cys
			20					25					30		

Tyr	Ser	Lys	Cys	Gly	Leu	His	Thr	Ser	Asn	Gly	Lys	Ser	Ser	Val	His
		35					40					45			

Thr	Val	Xaa
50		

&lt;210&gt; 182

&lt;211&gt; 91

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

100

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (91)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 182

Met	Leu	Arg	Cys	Ser	Phe	Ser	Ser	Phe	Leu	Leu	Cys	His	Thr	Ile	Leu
1				5					10					15	

Leu	Phe	Leu	Gly	Ser	Ser	Ala	His	Leu	Leu	Val	Glu	Xaa	Xaa	Val	Trp
			20					25						30	

Gly	Leu	Tyr	Glu	Tyr	Arg	Ile	Gly	Asp	Met	Val	Asp	Gln	Lys	Ala	Thr
		35					40						45		

Phe	Cys	Val	Gln	Lys	Gln	Glu	Cys	Leu	Phe	Pro	Leu	Gly	Ser	Trp	Val
	50					55					60				

Xaa	Arg	Val	Glu	Gly	Gly	Ala	Phe	Ala	Arg	Glu	Pro	Pro	Ser	Ser	Thr
65					70					75					80

Gln	Tyr	Phe	Pro	Val	Ser	Cys	Leu	Tyr	Gln	Xaa
				85					90	

&lt;210&gt; 183

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 183

Met	Ser	Ala	Leu	Leu	Ser	His	His	Val	Pro	Leu	Phe	Tyr	Leu	Thr	Gly
1				5					10					15	

Cys	Leu	Phe	Ser	Leu	Leu	Ala	Ser	Trp	Asp	Cys	Asn	Gly	Lys	Glu	Gly
			20					25					30		

Ala	Gly	Arg	Ala	Ile	Lys	Gly	Lys	Asn	Asn	Thr	Trp	Asn	Cys	Met	Ile
		35					40						45		

Leu	Ser	Lys	Val	Lys	Phe	Xaa
	50					55

&lt;210&gt; 184

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

101

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 184

Met	Val	His	Lys	Ala	Ile	Leu	Ala	Leu	Leu	Pro	Trp	Gly	Phe	Ser	Ala
1				5					10					15	

Asp	Glu	Leu	Leu	Ala	Ser	Leu	Met	Met	Xaa	Leu	Thr	Glu	Lys	Tyr	Gln
		20						25					30		

Asn	Cys	Ser	Ser	Thr	Thr	Asp	Ile	Xaa	Asn	Gln	Gln	Leu	Arg	Ser	Leu
		35					40					45			

Gly	Gln	Asn	Phe	Met	Phe	Gln	Gln	Asn	Leu	Gln	Leu	Ile	Leu	Met	Xaa
	50					55					60				

&lt;210&gt; 185

&lt;211&gt; 113

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (113)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 185

Met	Met	Thr	Ser	Ser	Leu	Gly	Leu	Ser	Phe	Leu	Leu	Asn	Leu	Ile	Leu
1				5					10					15	

Gly	Met	Lys	Phe	Thr	Tyr	Leu	Ile	Pro	Gln	Asn	Lys	Tyr	Ile	Gln	Leu
		20						25					30		

Phe	Thr	Thr	Ile	Leu	Ser	Phe	Phe	Ser	Gly	Val	Leu	Ser	Leu	Leu	Glu
		35					40					45			

Cys	Lys	Leu	Ser	Thr	Ser	Ser	Cys	Thr	Cys	Leu	Asn	Ile	His	Lys	Ser
	50					55					60				

Asp	Asn	Glu	Cys	Lys	Glu	Ser	Glu	Asn	Ser	Ile	Glu	Asp	Ile	Ser	Leu
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Xaa

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<400> 186
Met Leu His Leu Thr Leu Tyr Leu His Phe Ile Leu Phe Val Phe Pro
 1             5             10             15

Ile Thr Ser Asn Phe Ser Ser Leu His Pro Phe Leu Phe Ile Ser Ser
      20             25             30

Gln Phe Thr Ser Cys Cys Gln Ile Asn Phe Pro Asn Ala Gln Ala Leu
      35             40             45

Ser Tyr His Glu Phe Leu Ile Ala Thr Tyr Asp Xaa
      50             55             60

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<400> 187
Met  Pro  Cys  Ile  Arg  Gly  Val  Phe  His  Cys  Phe  Ile  Leu  Ile  Ile  Leu
  1              5              10              15

Ile  Leu  Leu  Ala  Ser  His  Ala  Phe  Ser  Gly  Ser  Gly  Asn  Gln  Arg  Leu
                20              25              30

Lys  Glu  Ala  Leu  Thr  Leu  Ile  Val  Ser  Val  Asn  Val  Asp  Ile  Ala  Arg
          35              40              45

His  Arg  Pro  Phe  Leu  Glu  Arg  Ile  His  Val  Lys  Lys  Gly  Asn  Thr  Xaa
      50              55              60

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103

<210> 188  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (71)  
 <223> Xaa equals stop translation

<400> 188  
 Met Phe Ser Arg Leu His Phe Leu Thr His Ser Leu Ser Leu Leu His  
           1                  5                  10                  15  
 Leu Pro Ser Gln Val Phe Gly Glu Val His Ser Ser Cys Val Ser Ser  
                   20                  25                  30  
 Leu Pro Cys Pro Asp Thr Pro Ala Leu Pro Tyr Cys Pro Ser Phe Leu  
                   35                  40                  45  
 Arg Tyr Asp Asp His Ile Glu Ala Gln Pro Leu Lys His Ile Asn Thr  
           50                  55                  60  
 Asn Asp His Ile Ser Ile Xaa  
           65                  70

<210> 189  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (63)  
 <223> Xaa equals stop translation

<400> 189  
 Met Cys Val Phe Ser Ser Asp Ser Ile Pro Ser Leu Leu Ile Leu Leu  
           1                  5                  10                  15  
 Val Leu Cys His Ser Val Cys Cys Leu Lys Leu Phe Phe Lys Leu Ile  
                   20                  25                  30  
 Phe Pro Asn Ser Phe Ile Ile Tyr Glu Lys Leu Gly Leu Asn His Phe  
                   35                  40                  45  
 Ala Tyr His Leu Ser Gly Trp Phe Glu Leu Ser Leu Asp Thr Xaa  
           50                  55                  60

<210> 190  
 <211> 193

<212> PRT  
 <213> Homo sapiens

14

<220>  
 <221> SITE  
 <222> (193)  
 <223> Xaa equals stop translation

<400> 190

Met	Glu	Ala	Leu	Leu	Gln	Ser	Leu	Val	Ile	Val	Leu	Leu	Gly	Phe	Lys	1	5	10	15
Ser	Phe	Leu	Ser	Glu	Glu	Leu	Gly	Ser	Glu	Val	Leu	Asn	Leu	Leu	Thr	20	25	30	
Asn	Lys	Gln	Tyr	Glu	Leu	Leu	Ser	Lys	Asn	Leu	Arg	Lys	Thr	Arg	Glu	35	40	45	
Leu	Phe	Val	His	Gly	Leu	Pro	Gly	Ser	Gly	Lys	Thr	Ile	Leu	Ala	Leu	50	55	60	
Arg	Ile	Met	Glu	Lys	Ile	Arg	Asn	Val	Phe	His	Cys	Glu	Pro	Ala	Asn	65	70	75	80
Ile	Leu	Tyr	Ile	Cys	Glu	Asn	Gln	Pro	Leu	Lys	Lys	Leu	Val	Ser	Phe	85	90	95	
Ser	Lys	Lys	Asn	Ile	Cys	Gln	Pro	Val	Thr	Arg	Lys	Thr	Phe	Met	Lys	100	105	110	
Asn	Asn	Phe	Glu	His	Ile	Gln	His	Ile	Ile	Ile	Asp	Asp	Ala	Gln	Asn	115	120	125	
Phe	Arg	Thr	Glu	Asp	Gly	Asp	Trp	Tyr	Gly	Lys	Ala	Lys	Phe	Ile	Thr	130	135	140	
Gln	Thr	Ala	Arg	Asp	Gly	Pro	Gly	Val	Leu	Trp	Ile	Phe	Leu	Asp	Tyr	145	150	155	160
Phe	Gln	Thr	Tyr	His	Leu	Ser	Cys	Ser	Ala	Ser	Pro	Leu	Pro	Gln	Thr	165	170	175	
Ser	Ile	Gln	Glu	Lys	Arg	Ser	Thr	Glu	Trp	Ser	Ala	Met	Gln	Val	Gln	180	185	190	

Xaa

<210> 191  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (112)  
 <223> Xaa equals stop translation

105

<400> 191  
Met Gln Phe Ser Leu Cys Leu Thr Ala Val Phe Leu Leu Gln Leu Ala  
1 5 10 15  
Ala Gly Ile Leu Gly Phe Val Phe Ser Asp Lys Ala Arg Gly Lys Val  
20 25 30  
Ser Glu Ile Ile Asn Asn Ala Ile Val His Tyr Arg Asp Asp Leu Asp  
35 40 45  
Leu Gln Asn Leu Ile Asp Phe Gly Gln Lys Lys Val Trp Val Ser Gln  
50 55 60  
Trp Ser Gly Gly Leu Trp Val Lys Val Asn Val Ile Pro Arg Asp Ala  
65 70 75 80  
Ser Pro Ser Met Pro Val Gly Leu Phe Ile Thr Cys Gln Val Met Ala  
85 90 95  
Ser Gly Lys Gly Phe Gly Lys Lys Ser Thr Arg Ser Arg Val Leu Xaa  
100 105 110

<210> 192  
<211> 80  
<212> PRT  
<213> Homo sapiens  
  
<220>  
<221> SITE  
<222> (80)  
<223> Xaa equals stop translation

<400> 192  
Met Cys Arg Pro Leu Leu Pro Leu Leu Phe Pro Trp Gly His Cys Leu  
1 5 10 15  
Ser Ile Pro Leu Cys Lys Trp Pro Gln Ile Met Ser Gln Pro Pro Arg  
20 25 30  
Leu His Arg Leu Leu Ala Ser Gly Pro Ser Thr Lys Lys His Ser Lys  
35 40 45  
Leu Gln Thr His Ser Trp Glu Asn Ser Asn Gly Leu Thr Leu Pro Phe  
50 55 60  
Glu Pro Ala Arg Ser His Gly Leu Trp Arg Ala Ala Phe Glu Ser Xaa  
65 70 75 80

<210> 193

<211> 88  
<212> PRT  
<213> Homo sapiens

106

<220>  
<221> SITE  
<222> (88)  
<223> Xaa equals stop translation

&lt;400&gt; 193

Met Leu Ser Ile Ile Asp Leu Leu Phe Leu Leu Ser Pro Thr Phe Gly  
1 5 10 15

Leu Ile Thr Glu Leu Leu Phe Ser Pro Glu Val Pro Lys Ala Leu Ser  
20 25 30

Cys Pro Leu Lys Ala Leu Gly Gly Gly Ser His Ser His Glu Pro Leu  
35 40 45

Gly Met Phe Ala Pro Val Pro Pro Gly Cys Glu Ser Ser Thr Pro Phe  
50 55 60

Pro Lys Gly Leu Gly Ala Ser Lys Ile Leu Thr Leu Gly Ala Gln Ala  
65 70 75 80

Glu Phe Arg Arg Arg Ser His Xaa  
85

<210> 194  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

&lt;400&gt; 194

Met Glu Asp His Phe Leu Ile Gly His Phe Pro Phe Phe Phe Leu Phe  
1 5 10 15

Ser Phe Pro Cys Phe Cys Thr Lys Pro Leu Cys Arg Glu Tyr Phe Leu  
20 25 30

Ile Cys Ser Ile Gln Asp Glu Ser Lys Xaa  
35 40

<210> 195  
<211> 69  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (69)

<223> Xaa equals stop translation 107

<400> 195

Met Phe Asn Leu Pro Lys Pro Val Phe Leu Ser Trp Trp Arg Trp Lys  
1 5 10 15

Thr Ile Val Ile Phe Leu Ala Cys Leu Ala Ser Ala Ala Ile Lys Glu  
20 25 30

Thr Ala Val Ser Met Lys Thr Val Phe Pro Ile Phe Val Gln Ile Thr  
35 40 45

Leu Ile Leu Leu Leu Glu Ser Arg Val Leu Lys Ile Gly Asp Phe Ser  
50 55 60

Asn Phe Phe Cys Xaa  
65

<210> 196

<211> 153

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (81)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (86)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (87)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

108

<220>  
 <221> SITE  
 <222> (103)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (110)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (153)  
 <223> Xaa equals stop translation

<400> 196  
 Met Asp His Ser Pro Thr Thr Gly Val Val Thr Val Ile Val Ile Leu  
 1 5 10 15  
 Ile Ala Ile Ala Ala Leu Gly Ala Phe Asp Pro Gly Leu Leu Val Leu  
 20 25 30  
 Pro Ala Ala Ala Ala His Gln Pro Val Arg Gly Arg Gly Glu His Arg  
 35 40 45  
 Gly Gly Trp Gly Asp Gln Gly Thr Leu Pro Ala Gly Ala Val Phe Gly  
 50 55 60  
 Gln Xaa Thr Val Arg Gly Glu Lys Gly Gln Ala Asp Xaa Ser Gln Thr  
 65 70 75 80  
 Xaa Arg Lys Xaa Thr Xaa Xaa Pro Gly Cys Lys Gly Xaa Leu Val Pro  
 85 90 95  
 Val Cys Lys Pro Ala Lys Xaa Gly Leu Gly Gly Ala Lys Xaa Ile Arg  
 100 105 110  
 Met Arg Cys Cys Leu Arg Gly Arg Ala Asp Thr Cys Trp His Gly Leu  
 115 120 125  
 Cys Gly Phe Arg Pro Ser His Ala Leu Met Pro Gly Asp Leu Ala Val  
 130 135 140  
 Leu Gly Phe Pro Ser Ala Ser Arg Xaa  
 145 150

<210> 197  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (63)  
 <223> Xaa equals stop translation

&lt;400&gt; 197

109

Met Lys Asn Ser Thr Ser Leu Leu Tyr Lys Leu Phe Ser Ser Leu Ser  
 1 5 10 15

Val Phe Ile Phe Lys Phe Leu Leu Leu Phe Tyr Thr Leu His Ile Ala  
 20 25 30

Leu Gly Val Lys Ile Gln Tyr Lys Pro Leu Ala His Phe Ile Asp His  
 35 40 45

Ser Cys Ile Gln Gln Val Ser Gln Val Gln Trp Ser Ile Pro Xaa  
 50 55 60

&lt;210&gt; 198

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 198

Met Gln Glu Pro His Gly Lys Phe Leu Ser Trp Gly Arg Trp Leu Trp  
 1 5 10 15

Trp Trp Ser Leu Ala Ala Pro Ala Leu Val Gln Ala Val Asn Met Pro  
 20 25 30

Pro Ala Tyr Ile Gln Ile Glu Asn Trp Tyr Met Met Leu Leu Met Gly  
 35 40 45

Trp Glu Thr Lys Cys Cys His Val Arg Ser Leu Trp Val Gly Thr Xaa  
 50 55 60

&lt;210&gt; 199

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 199

Met Leu Ile Asn Cys Ile Phe Ser Leu Leu Leu Leu Ser His Ala  
 1 5 10 15

Asp Gly Met His Leu Phe Ile Ser Ser Gly Asp Arg Ile Leu Phe Cys  
 20 25 30

Leu Tyr Phe Leu His Ser Arg Val Cys Ala Xaa  
35 40

<210> 200  
<211> 41  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (41)  
<223> Xaa equals stop translation

<400> 200  
Met Ser Val Tyr Val Asn Ile Met His Ile Val Ile Tyr Ile Tyr Leu  
1 5 10 15

Cys Val Tyr Met Cys Val Ala Gln Ser His Thr His Thr Gln Ile Cys  
20 25 30

Ile Gln Met Leu Pro Gly Leu Gln Xaa  
35 40

<210> 201  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 201  
Met Ile Leu Ser Phe Leu Met Leu Phe Leu Ile Val Lys Thr Ile Pro  
1 5 10 15

Leu Ile Leu Ala Tyr Cys Tyr Asn Ser Ile Ser Phe Phe Ser Asn Asn  
20 25 30

Leu Val Leu Val Lys Met Gly Tyr Asn Asn Lys Xaa  
35 40

<210> 202  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

<400> 202  
Met Arg Leu Leu Ser Thr Leu Leu Ser Phe Tyr Pro Phe Ser Asn Cys

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<220>
<221> SITE
<222> (113)

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<223> Xaa equals stop translation 112

<400> 204

Met Ala Pro Trp Leu Pro Leu Leu Ser Leu Leu Gly Leu Leu Leu Gly  
1 5 10 15

Xaa Ala Pro Ala Pro Pro Arg Arg Ala Ala Asp Ala Gln Ala Arg Glu  
20 25 30

Ala Ala Tyr Pro Glu Leu Leu Gly Pro Ala Arg Phe Ala Leu Glu Met  
35 40 45

Tyr Asn Arg Gly Arg Ala Ala Gly Xaa Arg Ala Thr Leu Gly Ala Val  
50 55 60

Arg Gly Arg Val Arg Arg Ala Gly Glu Gly Ser Leu Tyr Ser Leu Arg  
65 70 75 80

Ala Thr Leu Glu Glu Pro Pro Cys Asn Xaa Xaa Thr Val Cys Gln Leu  
85 90 95

Pro Val Ser Lys Arg Pro Cys Ser Ala Ala Leu Lys Ser Trp Thr Ser  
100 105 110

Xaa

<210> 205

<211> 45

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (45)

<223> Xaa equals stop translation

<400> 205

Met Pro Thr Trp Pro Leu Leu Gln Leu Leu Ser Cys Ser Phe Pro Ser  
1 5 10 15

Leu Leu Cys Glu Thr Phe Thr Phe Cys Ser Lys Asp Glu Val Ser Arg  
20 25 30

Trp Lys Ala Gly Cys Phe Val Pro Leu Pro Ala Ser Xaa  
35 40 45

<210> 206

<211> 71

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (71)

<223> Xaa equals stop translation

<400> 206 113  
 Met Thr His Trp Ser Gly Cys Ala Ala Leu Tyr Leu Ile Phe Leu Ser  
           1                  5                  10                  15  
 Leu Lys Leu Ala Phe Gln Ala Gly Ala Gly Arg Gly Ala Gln Val Gly  
                   20                  25                  30  
 Ser Val Leu Pro Pro Ser Gly Gly Ala Val Val Val Asp Gln Tyr Cys  
           35                  40                  45  
 Cys Arg Leu Ser Ala Gln Thr Tyr Phe Ser Leu Pro Ala Leu Gln Lys  
           50                  55                  60  
 Cys Ile Gly Ile Cys Arg Xaa  
           65                  70

<210> 207  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 207  
 Met Ile Asn Phe Trp Pro Val Thr His Val Cys Ile Trp Leu Leu Trp  
           1                  5                  10                  15  
 Leu Gln Ala Leu Glu Ala Arg Gly Gln Gly Ser Asn Ile Asp Cys Thr  
                   20                  25                  30  
 Arg Asn Ser Lys Thr Val Phe Thr Ser Xaa  
           35                  40

<210> 208  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (51)  
 <223> Xaa equals stop translation

<400> 208  
 Met Tyr Ile Tyr Leu Ile His Leu Cys Met Cys Val Tyr Ile Tyr Ile  
           1                  5                  10                  15  
 Tyr Ile Leu Leu Ile Ile Tyr Thr Leu Asp Pro Glu Pro Pro Ser Trp  
                   20                  25                  30  
 Ser Pro Lys Leu Asp Ser His Leu Ser Leu Arg Gln Pro Ser Asn Asp  
           35                  40                  45

Arg Phe Xaa  
50

114

<210> 209  
<211> 65  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (65)  
<223> Xaa equals stop translation

<400> 209  
Met Phe Val Leu Cys Thr Arg Ala Val Arg Thr Arg Leu Phe Ser Leu  
1 5 10 15  
Cys Cys Cys Cys Cys Ser Ser Gln Pro Pro Thr Lys Ser Pro Ala Gly  
20 25 30  
Thr Pro Lys Ala Pro Ala Pro Ser Lys Pro Gly Glu Ser Gln Glu Ser  
35 40 45  
Gln Gly Thr Pro Gly Glu Leu Pro Ser Thr Trp Ser Phe Cys Pro Phe  
50 55 60

Xaa  
65

<210> 210  
<211> 77  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (77)  
<223> Xaa equals stop translation

<400> 210  
Met Leu Ala Leu Leu Val Gly Gly Leu Val Ala Ala Leu Ala Cys His  
1 5 10 15  
Gly Ile Leu Ala Ala Ile Leu Ala Val Cys Gly Glu Leu Val Ser Gly  
20 25 30  
Lys Gly Thr Arg Ser Ser Asp Glu Asp Asp Gly Gly Asp Gly Asp Arg  
35 40 45  
Gly His Arg Gly Leu Ser Leu Leu Asn Ser Ala Phe Gly His Met Gly  
50 55 60  
Asp Gly Asp Arg Lys Asp Asp Asn Ser Gly Thr Leu Xaa  
65 70 75

<210> 211  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

115

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 211  
 Met Phe Val Gly Thr Arg Val Leu Leu Val Pro Leu Pro Phe Phe Ser  
           1                  5                  10                  15  
 Ile Ser Gly Met Leu Ala Ile Asp Lys Tyr Leu His Lys Lys Leu Leu  
                   20                  25                  30  
 Leu Asn Glu Ile Ile Thr Thr Ser Thr Trp Ala Leu Xaa  
                   35                  40                  45

<210> 212  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 212  
 Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser  
           1                  5                  10                  15  
 Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Xaa Leu Arg Glu Glu Ser  
                   20                  25                  30  
 Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro  
                   35                  40                  45  
 Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg  
           50                  55                  60  
 Thr Xaa  
           65

<210> 213  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

116

<400> 213  
 Met Arg Leu Cys Thr Thr Trp Met Ala Val Lys Phe Leu Trp Trp Gly  
           1                  5                  10                  15  
 Met Thr Trp Ile Pro Ser Gly Lys Ala Cys Ser Trp Thr Gln Pro Leu  
                   20                  25                  30  
 Cys Ser Ser Gly Gly Trp Ser Ser Pro Thr His Leu Pro Thr Ser Leu  
                   35                  40                  45  
 Leu Leu Gly Trp Arg Ala Ser Leu Cys Met Lys Arg Ser Xaa  
           50                  55                  60

<210> 214  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals stop translation

<400> 214  
 Met Phe Ala Ser Tyr His Ile Gln Phe Phe Thr Trp Leu Ile Gln Lys  
           1                  5                  10                  15  
 Leu Ser Leu Val Trp Lys Ser Val Val Ala Ile Arg Glu Gln Gly Lys  
                   20                  25                  30  
 Glu Leu Val Trp Lys Gln His Leu Pro Leu Arg Ser Tyr Ser Pro Asn  
           35                  40                  45  
 Asn Ala Lys Ser Leu Gly Leu Xaa  
           50                  55

<210> 215  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (88)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (213)  
 <223> Xaa equals stop translation

<400> 215  
 Met Leu Ser Phe Asn Phe Thr Trp Met Val Trp Val Ser Leu Val Leu  
 1 5 10 15  
 Lys Ser Gln Arg Ala Lys Leu Ala Leu His Ser Leu His Leu His Gln  
 20 25 30  
 Glu Val Arg Leu Arg Met Ser Arg Arg Glu Ser Pro Gly Arg Pro Leu  
 35 40 45  
 Arg Cys Gly Val Arg Gly Asn Met Gly Ala Arg Thr Pro Val Pro Thr  
 50 55 60  
 Ala Asp Tyr Pro Ser Pro Tyr Arg Thr Leu Pro Arg Met Ala Ala Pro  
 65 70 75 80  
 Pro Pro Gln Lys Ser Ser Cys Xaa Arg Leu His Arg Pro His Trp Trp  
 85 90 95  
 Arg Pro Arg Thr Pro Ser Ser Glu Lys Thr Gly Gly Gln Ser Gln Ser  
 100 105 110  
 Thr Leu Asp Arg Cys Ala His Leu Val His Met Leu Leu Arg Asp Gln  
 115 120 125  
 Arg Ala Thr Ser Gln Trp Lys Ala Gly Gly Arg Leu Cys Arg Ala Leu  
 130 135 140  
 Ser Lys Thr Pro Leu Gln His Gln Leu His Ser Thr Ser Tyr Arg Lys  
 145 150 155 160  
 Ala Leu Pro Ile Leu Arg Pro Ser Ser Arg Arg Glu Ala Gly Pro Leu  
 165 170 175  
 His His Ile Asp Leu Arg Arg Cys Phe Ser Arg Leu Gly Arg Gly Ala  
 180 185 190  
 Asp Phe Ala Val Cys Ala Lys Glu Pro Val Ser Asp Asn Pro Ile Phe  
 195 200 205  
 Leu Leu Ile Thr Xaa  
 210

<210> 216

<211> 41

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals stop translation

<400> 216

Met Asn Met Phe Gln Thr Ile Leu Val Cys Val Leu Phe Val Phe Val  
 1 5 10 15

118

Arg Trp Phe Phe Leu Leu Leu Gln Ile Glu Ser Ile Gln Thr Lys Phe  
                     20                    25                    30

His Cys Ile Ser Ser Gln Phe Trp Xaa  
                     35                    40

&lt;210&gt; 217

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (60)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 217

Met Glu Leu Val Trp Phe Arg Phe Leu His Leu Asn Leu Leu Pro Arg  
     1                    5                    10                    15

Gly Val Cys Cys Gly Ile Cys Val Cys Val Arg Arg Gly Met Val Leu  
                     20                    25                    30

Ser Glu Pro Thr Ser Cys Gly Gln Arg Ala Leu Ser Cys Glu Gly Gly  
                     35                    40                    45

Cys His Ser Gly Arg Val Gln Phe Arg Arg Pro Xaa  
                     50                    55                    60

&lt;210&gt; 218

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (59)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 218

Met Arg Arg Met Arg Met Lys Ser Leu Ser Pro Arg Arg Ser Trp Trp  
     1                    5                    10                    15

Thr Leu Trp Leu Gly Gln Gly Val Leu Gly Ala Ala Leu Lys Ala Asn  
                     20                    25                    30

Thr Leu Trp Ile Ala Met Arg Arg Arg Met Met Met Met Gly Gly Pro  
                     35                    40                    45

Ala Asn Met Thr Ser Trp Pro Gln Arg Met Xaa  
                     50                    55

&lt;210&gt; 219

&lt;211&gt; 46

<212> PRT  
 <213> Homo sapiens

119

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals stop translation

<400> 219

Met	Pro	Phe	Phe	Leu	Leu	Thr	Phe	Pro	Leu	Val	Leu	Tyr	Pro	His	Leu
1				5					10					15	
Ser	Arg	Gly	Ser	Asp	Pro	Val	Leu	Pro	Cys	Val	Met	Gly	Ile	His	Val
			20					25					30		
Phe	Gly	Leu	Ser	His	His	Ser	Arg	Lys	Val	Ala	Pro	Pro	Xaa		
		35					40					45			

<210> 220  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

<400> 220

Met	Asp	Arg	Val	Arg	Phe	Arg	Ser	Trp	Leu	Leu	Tyr	Pro	Cys	Cys	Val
1				5					10					15	
Ala	Leu	Gly	Gln	Glu	Leu	Gly	Leu	Ser	Ala	Pro	Gln	Trp	Leu	Ile	Thr
			20					25					30		
Glu	Asn	Gly	Met	Pro	Ala	Leu	Ala	Leu	Val	Gly	Cys	Phe	Glu	Pro	Thr
		35					40					45			
Ala	Gly	Ser	Gly	Ser	Ser	Trp	His	Asp	Val	Phe	Leu	Pro	Xaa		
		50				55					60				

<210> 221  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (52)  
 <223> Xaa equals stop translation

<400> 221

Met	Lys	Leu	Asn	Val	His	Phe	Leu	Trp	Cys	Thr	Phe	Ile	Phe	Gln	Thr
1				5					10					15	
Ser	Gly	Ser	His	Ile	Glu	Leu	Leu	Ile	Ser	Gly	Gln	Val	Ser	Ser	Tyr

20 25 30  
 120  
 Ile Pro Ser Leu Asp Phe Cys Thr His Lys Val Val Ser Arg Glu Lys  
 35 40 45

Phe Glu Glu Xaa  
 50

<210> 222  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (51)  
 <223> Xaa equals stop translation

<400> 222  
 Met Ala Ser Pro Val Phe Lys Thr Phe Trp Arg Leu Glu Leu Ser Val  
 1 5 10 15

Pro Leu Ser Leu Leu Phe Ile Leu Gln Ile Val Thr Ser Leu Ser Ser  
 20 25 30

Asp Glu Ile Cys Tyr Ser Thr Arg Lys Val Phe Ile Ile Arg Arg Gln  
 35 40 45

Leu Tyr Xaa  
 50

<210> 223  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals stop translation

<400> 223  
 Met Cys Met Cys Val Gly Val Cys Leu Ile Thr Leu Leu Asp Arg Phe  
 1 5 10 15

Leu Trp Phe Gly Thr Ala Gly Ala Lys Phe Ile Gln Lys Ser Thr Phe  
 20 25 30

Leu Ser Lys Leu Pro Met Thr Leu Val Ser Phe His Ser Ile Xaa  
 35 40 45

<210> 224  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

121

<220>  
 <221> SITE  
 <222> (52)  
 <223> Xaa equals stop translation

<400> 224  
 Met Cys Pro Phe His Lys Ala Tyr Leu Asp Cys Phe Phe Gln Ile Ser  
       1                  5                  10                  15  
 Leu Leu Leu Leu Ile Phe Leu Thr Tyr Leu Asp Ile Gly Lys Cys Gly  
                   20                  25                  30  
 Leu Trp Ser His Glu Trp Arg Ile Arg Glu Leu Gly Lys His Glu Arg  
           35                  40                  45  
 Trp Trp Asn Xaa  
       50

<210> 225  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 225  
 Met Asn Gln Pro Ile Leu Arg Ser Gln Ala Leu Leu Trp Pro Trp Arg  
       1                  5                  10                  15  
 Trp Val Val Lys Ala Lys Pro Cys Val Cys Val Ser Met Asp Ala Trp  
           20                  25                  30  
 Ile Pro Asp Arg Ser Gln His Cys Pro Ser Ile Pro Gly Gln Lys Lys  
           35                  40                  45  
 Glu Arg Ala Gly Ser His Gly His Gln Ala Leu Ala Xaa Leu Leu Phe  
       50                  55                  60  
 Leu Xaa  
       65

<210> 226  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<220>

<221> SITE  
 <222> (47)  
 <223> Xaa equals stop translation

122

<400> 226

Met Ala Ser Arg Gly Thr Ala Ala Pro Gly Arg Thr Phe Leu Ala Met  
 1 5 10 15

Met Val Thr Ser Phe Phe Phe Cys Met Arg Trp Gly Ser Trp Ala Glu  
 20 25 30

Gln Met Pro Gln Arg Cys Leu Pro Cys Cys Met Gln Glu Cys Xaa  
 35 40 45

<210> 227  
 <211> 222  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (184)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (222)  
 <223> Xaa equals stop translation

<400> 227

Met Ala Gly Gly Val Arg Pro Leu Arg Gly Leu Arg Ala Leu Cys Arg  
 1 5 10 15

Val Leu Leu Phe Leu Ser Gln Phe Cys Ile Leu Ser Gly Gly Glu Ser  
 20 25 30

Thr Glu Ile Pro Pro Tyr Val Met Lys Cys Pro Ser Asn Gly Leu Cys  
 35 40 45

Ser Arg Leu Pro Ala Asp Cys Ile Asp Cys Thr Thr Asn Phe Ser Cys  
 50 55 60

Thr Tyr Gly Lys Pro Val Thr Phe Asp Cys Ala Val Lys Pro Ser Val  
 65 70 75 80

Thr Cys Val Asp Gln Asp Phe Lys Ser Gln Lys Asn Phe Ile Ile Asn  
 85 90 95

Met Thr Cys Arg Phe Cys Trp Gln Leu Pro Glu Thr Asp Tyr Glu Cys  
 100 105 110

Thr Asn Ser Thr Ser Cys Met Thr Val Ser Cys Pro Arg Gln Arg Tyr  
 115 120 125

Pro Ala Asn Cys Thr Val Arg Asp His Val His Cys Leu Gly Asn Arg  
 130 135 140

123

Thr	Phe	Pro	Lys	Met	Leu	Tyr	Cys	Asn	Trp	Thr	Gly	Gly	Tyr	Lys	Trp
145					150					155					160
Ser	Thr	Ala	Leu	Ala	Leu	Ser	Ile	Thr	Leu	Gly	Gly	Phe	Gly	Ala	Asp
			165						170					175	
Arg	Phe	Tyr	Leu	Gly	Gln	Trp	Xaa	Glu	Gly	Leu	Gly	Lys	Leu	Phe	Ser
			180					185						190	
Phe	Gly	Gly	Leu	Gly	Ile	Trp	Thr	Leu	Ile	Asp	Val	Leu	Leu	Ile	Gly
			195				200						205		
Val	Gly	Tyr	Val	Gly	Pro	Ala	Asp	Gly	Ser	Leu	Tyr	Ile	Xaa		
	210					215					220				

<210> 228  
 <211> 49  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (49)  
 <223> Xaa equals stop translation

<400> 228

Met	Cys	Ile	His	Tyr	Ser	Arg	Val	Ile	Phe	Ser	Phe	Leu	Lys	Leu	Arg
1					5				10					15	
Ile	Lys	Ser	Ile	Ser	Trp	Tyr	Ala	Met	Trp	Leu	Tyr	Phe	Phe	Cys	Tyr
			20					25					30		
Leu	Asn	Cys	Leu	Ala	Lys	Val	Arg	Ser	Ala	Thr	Thr	Tyr	Leu	Tyr	Val
		35					40					45			

Xaa

<210> 229  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals stop translation

<400> 229

Met	Leu	Pro	Val	Cys	Val	Phe	Lys	Leu	Leu	Leu	Tyr	Leu	Tyr	Val	Leu
1				5					10					15	
Ile	Arg	Ile	Cys	Thr	Ile	Ile	Trp	Cys	Phe	Lys	Val	Tyr	Ile	Asn	Ala
			20					25					30		
Val	Ile	Leu	Asn	Lys	Ser	Ser	Arg	Xaa							

35

40

124

<210> 230  
<211> 53  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (53)  
<223> Xaa equals stop translation

<400> 230  
Met Asn Cys Gly Gly Ser Thr Leu Cys Val Leu Ser Phe Cys Ser Val  
1 5 10 15

Val Cys Ser Val Glu Ala Ser Cys Gln Ser Thr Val Gln Trp Gly Gly  
20 25 30

Ala Ala Ala Arg Val Gly Val Pro Phe Asp Trp Ser Arg Asn Glu Gln  
35 40 45

Gly Lys Gly His Xaa  
50

<210> 231  
<211> 50  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (45)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals stop translation

<400> 231  
Met Leu Gly Ser Ile Pro Lys Leu Trp Ser Val Leu Ser Phe Ser Ile  
1 5 10 15

Asn Phe Cys Phe Cys Cys Phe Ile Leu Ser Leu Leu Cys Leu Ser Val  
20 25 30

Leu Ser Asn Tyr Leu Phe Lys Thr Pro Arg Thr Trp Xaa Thr Leu His  
35 40 45

Arg Xaa  
50

<210> 232  
<211> 45

<212> PRT  
<213> Homo sapiens

125

<220>  
<221> SITE  
<222> (16)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (45)  
<223> Xaa equals stop translation

<400> 232  
Met Cys Leu Pro Leu Leu His Cys Thr Gly Ala Leu Trp Gly Lys Xaa  
1 5 10 15  
Val Leu Leu Phe Leu Tyr Cys Leu Ala Gln Ser Phe Ala Tyr Ser Arg  
20 25 30  
His Gln Thr Val Gly Leu Val Val His Asp Tyr Trp Xaa  
35 40 45

<210> 233  
<211> 55  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (55)  
<223> Xaa equals stop translation

<400> 233  
Met Cys Trp Ile Cys Val Trp Leu Phe Phe Ser Pro Thr Lys Thr Ser  
1 5 10 15  
Cys Phe Pro Trp Leu Ile Arg Pro Gly Pro Arg Ser Phe Thr Asp Ser  
20 25 30  
His Gly Thr Pro Pro Trp Gln Cys Leu Glu Pro Ser Ser Phe Thr Tyr  
35 40 45  
Pro Gly Lys Gln Val Trp Xaa  
50 55

<210> 234  
<211> 69  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (69)  
<223> Xaa equals stop translation

<400> 234 126  
 Met Lys Arg Leu Arg Phe Val Leu Arg Val Phe Gln Met Thr Ala Phe  
           1                          5                          10                          15  
 Ile Thr Gly Ala His Thr Ile Thr Asn Tyr Ser Asp Arg Arg Leu Tyr  
                           20                          25                          30  
 Ile Ser Pro Leu Ser His Phe Phe Met Asn Ser Gly Ser Ser Ala Gln  
                           35                          40                          45  
 Ser Val Leu Ser His Ser Tyr Val Ser Gln Ile Phe Phe Lys Asn Val  
           50                          55                          60  
 Ser Lys Tyr Phe Xaa  
           65

<210> 235  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals stop translation

<400> 235  
 Met Val Ala Met Val Phe Leu Lys Ile Ser Val Leu Pro Leu Met Cys  
           1                          5                          10                          15  
 Arg Gly Gln Thr Lys His Lys Val Leu Arg Asp His Ala Tyr Pro Arg  
                           20                          25                          30  
 Val Ser Gln Lys Arg Gly His Ile Xaa  
           35                          40

<210> 236  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (34)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 236  
 Met Thr Lys Leu Leu Ser Leu Ser His Leu Leu Val Thr Phe Phe Asn  
           1                          5                          10                          15  
 Ile Ile Ala Ile Lys Cys Lys Lys Gln His Leu Arg His Ser Lys Cys

20

25

177

30

Asn Xaa Asp Thr Thr Phe Lys Asn Lys Met Leu Asn Xaa  
 35 40 45

&lt;210&gt; 237

&lt;211&gt; 78

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (78)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 237

Met Gln Leu Cys Val Ile Trp Phe Thr Val Ile Phe Leu Ser Gln Ser  
 1 5 10 15

Ser Arg Leu Val Lys Glu Lys Ile Ser Asn Thr Ser Gly Glu Lys Gly  
 20 25 30

Arg Trp Pro Ala Ile Asp Val Val Ala Leu Cys Pro Ser Arg Thr Ala  
 35 40 45

Gly Ile Ser Phe Pro Arg His Phe Leu Tyr Val Ser Cys Ile Val Gly  
 50 55 60

Cys Thr Asn Ile Ile Cys Ser Phe Gly Phe Pro Gly Gln Xaa  
 65 70 75

&lt;210&gt; 238

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 238

Met Glu Val Val Leu Pro Lys His Ile Leu Asp Ile Trp Val Ile Val  
 1 5 10 15

Leu Ile Ile Leu Ala Thr Ile Val Ile Met Thr Ser Leu Leu Leu Cys  
 20 25 30

Pro Ala Thr Ala Val Ile Ile Tyr Arg Met Arg Thr His Pro Ile Leu  
 35 40 45

Ser Gly Ala Val Xaa  
 50

&lt;210&gt; 239

<211> 53  
<212> PRT  
<213> Homo sapiens

128

<220>  
<221> SITE  
<222> (53)  
<223> Xaa equals stop translation

&lt;400&gt; 239

Met Tyr Tyr Leu Gly Lys Trp Asp Ile Trp Gln Pro Val Ser Leu Leu  
1 5 10 15

Tyr Ile Ile Leu Phe Ala Ala Cys Pro Ser Leu Leu Ile Ser Ile Pro  
20 25 30

Ala Lys Ala Ser Gly Glu Gly Trp Arg Cys Gly Asp Ile Gln Leu Thr  
35 40 45

Val Val Thr Asp Xaa  
50

<210> 240  
<211> 43  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (43)  
<223> Xaa equals stop translation

&lt;400&gt; 240

Met Pro Val Ala Phe His Leu Pro Phe Leu Leu Ile Leu Pro Tyr Arg  
1 5 10 15

Val Leu Pro Val Gly Gln Val Thr Gln Leu Thr Pro Arg Ala Val Glu  
20 25 30

Val Lys Ile His Asn His Gly Arg Leu Pro Xaa  
35 40

<210> 241  
<211> 49  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (49)  
<223> Xaa equals stop translation

&lt;400&gt; 241

Met Ser Trp Pro Leu Cys Thr Leu Leu Phe Ser Trp Asp Cys Ile Leu  
1 5 10 15

129

Ala Val Lys Thr Ser Arg Leu Lys Phe Asp Ser Gln Gly Tyr Ile Leu  
                     20                    25                    30

Gly Thr Phe Lys Val Ser Phe Gln Arg Asp Phe Ile Asn Arg Leu Asp  
                     35                    40                    45

Xaa

<210> 242  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals stop translation

<400> 242  
 Met Ser Ile Ile Ile Tyr Trp Leu Leu Phe Phe Lys His Leu Leu Trp  
       1                    5                    10                    15

Val Leu Ile Ile Gly Met Val Lys Ala Leu His Pro His Tyr Leu Asn  
                     20                    25                    30

Leu Arg Ile Tyr Glu Phe Gly Glu Ile Thr Ala Val Leu Gln Arg Lys  
                     35                    40                    45

Lys Gln Gly Arg Glu Asn Gly Asn Phe Leu Lys Phe Ser Leu Leu Ser  
                     50                    55                    60

Leu Asn Arg Ser Arg Ile Pro Thr Gln Ile Xaa  
       65                    70                    75

<210> 243  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals stop translation

<400> 243  
 Met Ala Ile His Phe His Ile Ile Gln Trp Leu Leu Leu Cys Tyr Asn  
       1                    5                    10                    15

Cys His His Ala Gln Trp Gly Leu Trp His Thr Thr Ala Glu Val Ser  
                     20                    25                    30

Gly Cys Gly Arg Asn His Leu Ala Phe Lys Ala Xaa  
                     35                    40

<210> 244  
 <211> 65  
 <212> PRT  
 <213> Homo sapiens

130

<220>  
 <221> SITE  
 <222> (65)  
 <223> Xaa equals stop translation

&lt;400&gt; 244

Met Tyr Leu Ser Leu Phe Phe Phe Cys Phe Ser Leu Gln Ala Ser Ala  
 1 5 10 15

Val Glu Glu Arg Ser Ala Glu Ser Ser Arg Glu Gly Pro Val Arg Thr  
 20 25 30

Asp Asn Trp Gln Arg Cys Phe Gly Asp Ile Pro Gly Thr Pro Thr His  
 35 40 45

Leu Val Gln Arg Ser Leu Val Leu Thr Cys Phe Gly Arg Val Leu Ser  
 50 55 60

Xaa  
 65

<210> 245  
 <211> 84  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (84)  
 <223> Xaa equals stop translation

&lt;400&gt; 245

Met Lys Lys Val Cys Trp Val Trp Ala Leu Ala His Leu Val Leu Cys  
 1 5 10 15

Glu Arg Trp Leu Thr Ala Gly Cys Leu Leu Tyr Val Gly Val Ile Gln  
 20 25 30

Pro Cys Lys Gly Ser Pro Ser Ser Val Cys Lys Ala Arg Arg Cys Leu  
 35 40 45

His Pro Lys Tyr Arg Ile Lys Arg Tyr Gly Tyr Tyr Lys Tyr Ser Val  
 50 55 60

Arg Leu Ile Ile Cys His His His Pro His Ala Leu Lys Ala Glu Leu  
 65 70 75 80

Thr Asp Asp Xaa

&lt;210&gt; 246

<211> 72  
 <212> PRT  
 <213> Homo sapiens

131

<220>  
 <221> SITE  
 <222> (72)  
 <223> Xaa equals stop translation

&lt;400&gt; 246

Met Val Gln Gly Pro Leu Thr His Leu Met Leu Val Leu Leu Ile Ser  
 1 5 10 15

Leu Ile Phe Leu Ser Arg Gly Ser Gly Arg Ala Trp Ala Phe Ser His  
 20 25 30

Ser Cys Phe Lys Thr Ser Asp Leu Leu Pro Cys Arg Asn Arg Trp Glu  
 35 40 45

Val Ile Glu Phe Leu His Tyr Ser Asn Leu His Ser His Ile Ser Leu  
 50 55 60

Ser Val Thr Lys Thr Phe Leu Xaa  
 65 70

<210> 247  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals stop translation

&lt;400&gt; 247

Met Arg Ser Tyr Phe Pro Phe Ser Val Cys Pro Phe Pro Phe Cys Ser  
 1 5 10 15

Pro Val Phe Phe Phe Val Phe Thr Asp Val Tyr Leu Cys Phe Phe Phe  
 20 25 30

Val Phe Ala Val Gly Arg His Leu Ser Asp Pro Phe Pro Ile Leu Phe  
 35 40 45

Phe Thr His Lys Cys Pro Asp Val Xaa  
 50 55

<210> 248  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (67)

<223> Xaa equals stop translation 132

<400> 248

Met Arg Ala Cys Gly Trp Asp Leu Ser Ile Leu Leu Val Gly Leu Val  
1 5 10 15

Met Gly Arg Glu Gly Cys Tyr Ser Arg Leu Pro Pro Thr Glu Tyr Gln  
20 25 30

Lys Gln Ala Gly Ser Ser Gly Val Cys Lys Asp Val Arg Pro Arg Asn  
35 40 45

Gln Pro Ser Pro Ser Tyr Pro Cys Lys Ser Leu Ser Pro His Ala Pro  
50 55 60

Leu Leu Xaa  
65

<210> 249

<211> 46

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (46)

<223> Xaa equals stop translation

<400> 249

Met Tyr Leu Ile Leu Ser Trp Leu Phe Leu Cys Lys Leu Val Lys Cys  
1 5 10 15

Tyr Phe Glu Ile Leu Leu Phe Ser Thr Ser Pro Gln Leu Leu Gln Trp  
20 25 30

Thr Val Ile Val Thr Tyr Cys Gly Pro Leu Leu Arg Phe Xaa  
35 40 45

<210> 250

<211> 54

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals stop translation

<400> 250

Met Leu Val Phe Leu Leu Leu Phe Ser Thr Val Thr Val Leu Cys Leu  
1 5 10 15

Lys Val Val Phe Ser Leu Lys Ala Val Ala Tyr Ile Val Lys Asn Glu  
20 25 30

Gly Leu Cys Leu Lys Phe Ile Ala Leu Gln Arg Val Val Ser Leu Lys

35

40

133

45

Ser Cys Thr Ile Lys Xaa  
50

&lt;210&gt; 251

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 251

Met Thr Phe Leu Leu Gln Trp Phe Pro Leu Gly Arg Ala Arg Val Val  
1 5 10 15

Gly Asp Leu Cys Gly Phe Ser Thr Gln Ile His Pro Gly Val Ser Arg  
20 25 30

Ala Gly Met Ala Asp Leu Glu Ser Pro Pro Phe Pro Arg Thr Cys Ser  
35 40 45

Val Pro Arg Ala Ala Asn Lys Gly Xaa  
50 55

&lt;210&gt; 252

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 252

Met Phe Val Lys Tyr His Val Ile Met Val Ile Ile Phe Ile Phe Ile  
1 5 10 15

Leu Ile Thr Ser Asp Lys His Gly Glu Ile Ile Tyr Ile Lys Tyr Ile  
20 25 30

Asp Arg Val Ile Ile Thr Glu Arg Ile Xaa  
35 40

&lt;210&gt; 253

&lt;211&gt; 161

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

134

&lt;222&gt; (161)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 253

Met Gln Arg Val Ser Gly Leu Leu Ser Trp Thr Leu Ser Arg Val Leu  
 1 5 10 15

Trp Leu Ser Gly Leu Ser Glu Pro Gly Ala Ala Arg Gln Pro Arg Ile  
 20 25 30

Met Glu Glu Lys Ala Leu Glu Val Tyr Asp Leu Ile Arg Thr Ile Arg  
 35 40 45

Asp Pro Glu Lys Pro Asn Thr Leu Glu Glu Leu Glu Val Val Ser Glu  
 50 55 60

Ser Cys Val Glu Val Gln Glu Ile Asn Glu Glu Glu Tyr Leu Val Ile  
 65 70 75 80

Ile Arg Phe Thr Pro Thr Val Pro His Cys Ser Leu Ala Thr Leu Ile  
 85 90 95

Gly Leu Cys Leu Arg Val Lys Leu Gln Arg Cys Leu Pro Phe Lys His  
 100 105 110

Lys Leu Glu Ile Tyr Ile Ser Glu Gly Thr His Ser Thr Glu Glu Asp  
 115 120 125

Ile Asn Lys Gln Ile Asn Asp Lys Glu Arg Val Ala Ala Ala Met Glu  
 130 135 140

Asn Pro Asn Leu Arg Glu Ile Val Glu Gln Cys Val Leu Glu Pro Asp  
 145 150 155 160

Xaa

&lt;210&gt; 254

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 254

Met Leu Phe Phe Ser Leu Lys Glu Ser Leu Tyr Ile Phe His Thr Ala  
 1 5 10 15

Ile Leu Leu Val Val Cys Phe Ala Cys Ala Val Val Cys Gln Tyr Val  
 20 25 30

Ile Val Arg Val Cys Ala Val Val Phe Cys Phe Ser Lys Ser Gln Ser  
 35 40 45

Leu Ile Xaa  
50

135

<210> 255  
<211> 279  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (279)  
<223> Xaa equals stop translation

<400> 255  
Met Leu Ile Phe Gly Ala Ile Phe Gly Cys Leu Asp Pro Val Ala Thr  
1 5 10 15  
Leu Ala Ala Val Met Thr Glu Lys Ser Pro Phe Thr Thr Pro Ile Gly  
20 25 30  
Arg Lys Asp Glu Ala Asp Leu Ala Lys Ser Ala Leu Ala Met Ala Asp  
35 40 45  
Ser Asp His Leu Thr Ile Tyr Asn Ala Tyr Leu Gly Trp Lys Lys Ala  
50 55 60  
Arg Gln Glu Gly Gly Tyr Arg Ser Glu Ile Thr Tyr Cys Arg Arg Asn  
65 70 75 80  
Phe Leu Asn Arg Thr Ser Leu Leu Thr Leu Glu Asp Val Lys Gln Glu  
85 90 95  
Leu Ile Lys Leu Val Lys Ala Ala Gly Phe Ser Ser Ser Thr Thr Ser  
100 105 110  
Thr Ser Trp Glu Gly Asn Arg Ala Ser Gln Thr Leu Ser Phe Gln Glu  
115 120 125  
Ile Ala Leu Leu Lys Ala Val Leu Val Ala Gly Leu Tyr Asp Asn Val  
130 135 140  
Gly Lys Ile Ile Tyr Thr Lys Ser Val Asp Val Thr Glu Lys Leu Ala  
145 150 155 160  
Cys Ile Val Glu Thr Ala Gln Gly Lys Ala Gln Val His Pro Ser Ser  
165 170 175  
Val Asn Arg Asp Leu Gln Thr His Gly Trp Leu Leu Tyr Gln Glu Lys  
180 185 190  
Ile Arg Tyr Ala Arg Val Tyr Leu Arg Glu Thr Thr Leu Ile Thr Pro  
195 200 205  
Phe Pro Val Leu Leu Phe Gly Gly Asp Ile Glu Val Gln His Arg Glu  
210 215 220  
Arg Leu Leu Ser Ile Asp Gly Trp Ile Tyr Phe Gln Ala Pro Val Lys

225 230 235 240  
 Ile Ala Val Ile Phe Lys Gln Leu Arg Val Leu Ile Asp Ser Val Leu  
 245 250 255  
 Arg Lys Lys Leu Glu Asn Pro Lys Met Ser Leu Glu Met Thr Arg Phe  
 260 265 270  
 Cys Arg Ser Leu Arg Asn Xaa  
 275

<210> 256  
 <211> 69  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (69)  
 <223> Xaa equals stop translation

<400> 256  
 Met Lys Val Leu Ser Trp Ile His Phe Ile Leu Ile Ser Leu His Phe  
 1 5 10 15  
 Thr Ser Ser Leu Asp Pro Ser Ser Arg Gly Leu Gly Thr Phe Thr Asp  
 20 25 30  
 Ala Leu Pro Asp Ser Arg Ala Lys Val Trp Glu Gly Glu Met Glu Glu  
 35 40 45  
 Cys Pro Pro Val Cys Val Val Leu Cys Ala Thr Ala Thr Asp Ala Glu  
 50 55 60  
 Gly Phe Ser Gly Xaa  
 65

<210> 257  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (122)  
 <223> Xaa equals stop translation

<400> 257  
 Met Ile Met Ala Gln Lys Ile Gly Gly Leu Thr Trp Trp Ala Ile Met  
 1 5 10 15  
 Phe Ile Ile Leu Phe Glu Ile Thr Gly Thr Ser Ser Ser Phe Leu Arg  
 20 25 30  
 Ile Asn Ala Leu Pro His Phe Ser Met Asn Arg Cys Gly Glu Ala Tyr  
 35 40 45

137

Phe Pro Phe Ser Tyr Leu Tyr Thr Ser Leu Gln Lys Gln Phe Leu Met  
 50 55 60

Lys Val Ser Gly Ile Val Lys Asn Leu Arg Gly Asn Asp Asp Trp Arg  
 65 70 75 80

Cys Phe Gly Val Phe Phe Cys Ile His Phe Leu Met Arg Lys Val Leu  
 85 90 95

Asn Val Val Gln Val Arg Pro Asn Tyr Tyr Leu Thr Ile Ile Gly Arg  
 100 105 110

Phe Tyr Val Ser Val Lys Val Phe Lys Xaa  
 115 120

<210> 258  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals stop translation

<400> 258  
 Met Gly Lys Ile Cys Lys Asn Trp Val Ser Phe Leu Asp Asn Val Leu  
 1 5 10 15

Leu Leu Ile Leu Phe Leu Tyr Gly Leu Cys Leu Gly Trp Leu Cys Ile  
 20 25 30

Tyr His Gln Ser Tyr Ser Thr Ala Cys Ile Cys Val Val Thr Asp Ala  
 35 40 45

Glu Ile Gln Gln Lys Ser Leu His Ser Ile Xaa  
 50 55

<210> 259  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (68)  
 <223> Xaa equals stop translation

<400> 259  
 Met Leu Val Leu Leu Trp Leu Gly Trp Ile Ser Ser Lys Ser Met Leu  
 1 5 10 15

Ala Ala Tyr Phe Val Ala Pro Lys Tyr Pro Leu Lys Leu Ala Leu Val  
 20 25 30

```

<400> 261
Phe Tyr Ile Ala Asp His Ser Phe Thr Ala Arg Pro Thr Leu Arg Met
 1             5             10             15
Phe Arg Ile Ser Ala Val Val Ala Thr Asp Lys Met Thr Phe Thr Ser
          20             25             30
Gly Gly Thr Leu Phe Gly Asp Gly Cys Ala Ser Ser Val Ala Gly Glu
      35             40             45
Val Met Asn Cys Gln Thr Val Leu Cys Ile Leu Trp Thr Pro Phe Val
      50             55             60
Phe Cys Pro Ser Ile Ala Val Ile Ile Ile Pro Cys Val Phe Thr Ser
 65             70             75             80
Lys Ala Leu Glu Ala Ile Trp Lys Trp Cys Arg Val Glu Arg Arg Pro
          85             90             95
His Ile Ile Glu Val Asp Val Leu Gly Lys Cys Pro Ala Phe
      100             105             110

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<210> 262  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 262  
 Arg Pro Thr Leu Arg Met Phe Arg Ile Ser Ala Val Val Ala Thr Asp  
       1                  5                  10                  15  
 Lys Met Thr Phe Thr Ser Gly Gly Thr  
                   20                  25

<210> 263  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 263  
 Pro Ser Ile Ala Val Ile Ile Ile Pro Cys Val Phe Thr Ser Lys Ala  
       1                  5                  10                  15  
 Leu Glu Ala Ile Trp Lys Trp Cys Arg Val Glu Arg  
                   20                  25

<210> 264  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

<400> 264  
 Thr Ser Val Ser Phe His His Arg Tyr Lys Ser Ser Asp Arg Pro Ala  
       1                  5                  10                  15  
 His Lys Val Ser  
                   20

<210> 265  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<400> 265  
 Arg His Asn Asp Phe Asn Lys Leu Ser Tyr Thr Glu Cys Asn Asn Met  
       1                  5                  10                  15  
 Asn Lys Arg Met Ala Lys Pro Glu Lys Lys Lys Gly Ser Val Lys Ser  
                   20                  25                  30  
 Ser Leu Gly Ile Phe Leu Gly Pro Asn Cys His Leu Ile Ser Ser Leu  
           35                  40                  45  
 Phe Leu Phe Ser Val Ser Leu Tyr Pro Phe Ala Thr Gln Phe Pro Phe  
       50                  55                  60

140

His Tyr Val Leu Ile Phe Ile Ile Gln Ala Phe Gly Leu Cys Leu Pro  
 65 70 75 80

Leu Thr Glu Arg Gln Glu Ala Lys Ser Gly Leu Gly Gly Leu Cys Pro  
 85 90 95

Asp Tyr Thr Trp Pro Cys Pro Cys Leu Leu Val Ser Cys Leu Ser Leu  
 100 105 110

Leu Arg Leu  
 115

<210> 266  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 266  
 Cys Glu Val Phe Ser Trp His Phe Pro Trp Ser Lys Leu Ser Pro His  
 1 5 10 15

Leu Phe Leu Val Ser Phe Leu Cys Ile Pro Leu Ser Leu Cys His Thr  
 20 25 30

Val Ser Phe Ser Leu Cys Ser Asn Ile Tyr Asn Pro Gly Leu Arg Thr  
 35 40 45

Met Leu Ala Pro His Arg Glu Thr Gly Gly Gln Val Trp Ala Gly Trp  
 50 55 60

Ala Leu Ser Arg Leu His Val Ala Leu Pro Met Ser Leu Gly Val Leu  
 65 70 75 80

Ser Leu Pro Ala Pro Thr Val Thr Val Val Arg Met Glu Gly Gly Asp  
 85 90 95

Trp Lys Val Cys Glu Gln Leu Gly Gln Cys Thr Tyr Ser His Arg Met  
 100 105 110

Thr Lys

<210> 267  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 267  
 Lys Arg Met Ala Lys Pro Glu Lys Lys Lys Gly Ser Val Lys Ser Ser  
 1 5 10 15

Leu Gly Ile Phe Leu Gly Pro  
 20

<210> 268

<211> 31  
 <212> PRT  
 <213> Homo sapiens

141

<400> 268  
 Tyr Asn Pro Gly Leu Arg Thr Met Leu Ala Pro His Arg Glu Thr Gly  
     1                    5                    10                    15  
 Gly Gln Val Trp Ala Gly Trp Ala Leu Ser Arg Leu His Val Ala  
                     20                    25                    30

<210> 269  
 <211> 251  
 <212> PRT  
 <213> Homo sapiens

<400> 269  
 Met Ser Pro Tyr Ala Ser Gln Gly Phe Pro Phe Leu Pro Pro Tyr Pro  
     1                    5                    10                    15  
 Pro Gln Glu Ala Asn Arg Ser Ile Thr Ser Leu Ser Val Ala Asp Thr  
                     20                    25                    30  
 Val Ser Ser Ser Thr Thr Ser His Thr Thr Ala Lys Pro Ala Ala Pro  
                     35                    40                    45  
 Ser Phe Gly Val Leu Ser Asn Leu Pro Leu Pro Ile Pro Thr Val Asp  
     50                    55                    60  
 Ala Ser Ile Pro Thr Ser Gln Asn Gly Phe Gly Tyr Lys Met Pro Asp  
     65                    70                    75                    80  
 Val Pro Asp Ala Phe Pro Glu Leu Ser Glu Leu Ser Val Ser Gln Leu  
                     85                    90                    95  
 Thr Asp Met Asn Glu Gln Glu Glu Val Leu Leu Glu Gln Phe Leu Thr  
                     100                    105                    110  
 Leu Pro Gln Leu Lys Gln Ile Ile Thr Asp Lys Asp Asp Leu Val Lys  
     115                    120                    125  
 Ser Ile Glu Glu Leu Ala Arg Lys Asn Leu Leu Leu Glu Pro Ser Leu  
     130                    135                    140  
 Glu Ala Lys Arg Gln Thr Val Leu Asp Lys Tyr Glu Leu Leu Thr Gln  
     145                    150                    155                    160  
 Met Lys Ser Thr Phe Glu Lys Lys Met Gln Arg Gln His Glu Leu Ser  
                     165                    170                    175  
 Glu Ser Cys Ser Ala Ser Ala Leu Gln Ala Arg Leu Lys Val Ala Ala  
                     180                    185                    190  
 His Glu Ala Glu Glu Glu Ser Asp Asn Ile Ala Glu Asp Phe Leu Glu  
     195                    200                    205  
 Gly Lys Met Glu Ile Asp Asp Phe Leu Ser Ser Phe Met Glu Lys Arg

210 215 192 220

Thr Ile Cys His Cys Arg Arg Ala Lys Glu Glu Lys Leu Gln Gln Ala  
 225 230 235 240

Ile Ala Met His Ser Gln Phe His Ala Pro Leu  
 245 250

<210> 270  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 270  
 Leu Pro Pro Tyr Pro Pro Gln Glu Ala Asn Arg Ser Ile Thr Ser Leu  
 1 5 10 15

Ser Val Ala Asp Thr Val Ser  
 20

<210> 271  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 271  
 Thr Ala Lys Pro Ala Ala Pro Ser Phe Gly Val Leu Ser Asn Leu Pro  
 1 5 10 15

Leu Pro Ile Pro Thr Val Asp Ala Ser Ile Pro  
 20 25

<210> 272  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 272  
 Pro Asp Val Pro Asp Ala Phe Pro Glu Leu Ser Glu Leu Ser Val Ser  
 1 5 10 15

Gln Leu Thr Asp Met Asn Glu Gln Glu  
 20 25

<210> 273  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 273  
 Gln Phe Leu Thr Leu Pro Gln Leu Lys Gln Ile Ile Thr Asp Lys Asp  
 1 5 10 15

Asp Leu Val Lys Ser Ile Glu Glu Leu Ala Arg Lys Asn

20

25

143

&lt;210&gt; 274

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 274

Arg Gln Thr Val Leu Asp Lys Tyr Glu Leu Leu Thr Gln Met Lys Ser  
1 5 10 15

Thr Phe Glu Lys Lys Met Gln Arg Gln  
20 25

&lt;210&gt; 275

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 275

Ala Ser Ala Leu Gln Ala Arg Leu Lys Val Ala Ala His Glu Ala Glu  
1 5 10 15

Glu Glu Ser Asp Asn Ile Ala Glu Asp Phe Leu Glu  
20 25

&lt;210&gt; 276

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 276

Met Glu Lys Arg Thr Ile Cys His Cys Arg Arg Ala Lys Glu Glu Lys  
1 5 10 15

Leu Gln Gln Ala Ile Ala Met His Ser Gln Phe  
20 25

&lt;210&gt; 277

&lt;211&gt; 69

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 277

Thr Arg Pro Val Phe Leu Ser Met Thr Pro Leu Lys Gly Ile Lys Ser  
1 5 10 15

Val Ile Leu Pro Gln Val Phe Leu Cys Ala Tyr Met Ala Ala Phe Asn  
20 25 30

Ser Ile Asn Gly Asn Arg Ser Tyr Thr Cys Lys Pro Leu Glu Arg Ser  
35 40 45

Leu Leu Met Ala Gly Ala Val Ala Ser Ser Thr Phe Leu Gly Val Ile

50 55 60  
 144

Pro Gln Phe Val Gln  
 65

<210> 278  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 278  
 Pro Leu Lys Gly Ile Lys Ser Val Ile Leu Pro Gln Val Phe Leu Cys  
 1 5 10 15

Ala Tyr Met Ala Ala  
 20

<210> 279  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 279  
 Ala Phe Asn Ser Ile Asn Gly Asn Arg Ser Tyr Thr Cys Lys Pro Leu  
 1 5 10 15

Glu Arg Ser Leu Leu  
 20

<210> 280  
 <211> 129  
 <212> PRT  
 <213> Homo sapiens

<400> 280  
 Met Ser Asp Phe Glu Lys Val Asp Ile Ser Val His Gln His Ile His  
 1 5 10 15

Val Gly Pro Leu Leu Leu Met Thr Thr Glu Ser Trp Gly Pro Ser Cys  
 20 25 30

Ala Pro Ser Pro Ala Leu Leu Ser Gly His Thr Ala Ala Ser Phe Thr  
 35 40 45

His Thr Leu Gly Gly Val Leu Gly Cys Pro Pro Tyr His Lys Phe Tyr  
 50 55 60

Ser Ser Ala His Thr Ser Asp His Arg Lys Glu Thr Asn Lys Val Glu  
 65 70 75 80

Glu Gly Arg Trp Val Asp Val Thr Arg Ser Leu Gly Asn Phe Asn Phe  
 85 90 95

Arg Arg Lys Phe Phe Cys Val Ser Glu Leu Leu Ile Cys Gly Ile Phe  
 100 105 110

145

Leu	Asp	Ser	Ser	Trp	Lys	Leu	Gln	Ile	Asn	Ser	Asn	Asp	Cys	Lys	Val
		115					120					125			

Leu

<210> 281

<211> 30

<212> PRT

<213> Homo sapiens

<400> 281

Val	Gly	Pro	Leu	Leu	Leu	Met	Thr	Thr	Glu	Ser	Trp	Gly	Pro	Ser	Cys
1				5					10					15	

Ala	Pro	Ser	Pro	Ala	Leu	Leu	Ser	Gly	His	Thr	Ala	Ala	Ser
			20					25					30

<210> 282

<211> 27

<212> PRT

<213> Homo sapiens

<400> 282

Glu	Thr	Asn	Lys	Val	Glu	Glu	Gly	Arg	Trp	Val	Asp	Val	Thr	Arg	Ser
1				5				10						15	

Leu	Gly	Asn	Phe	Asn	Phe	Arg	Arg	Lys	Phe	Phe
			20					25		

<210> 283

<211> 140

<212> PRT

<213> Homo sapiens

<400> 283

Gly	Arg	Gly	Asp	Lys	Pro	Arg	Gln	Asp	Arg	Pro	Ala	Ser	Leu	Arg	Leu
1				5				10					15		

Lys	Gly	Pro	Pro	Ser	Cys	Gln	Ala	Pro	Ala	Ser	His	Ser	Ser	Thr	Leu
			20					25					30		

Ser	Ser	His	Cys	Pro	Cys	Ser	Leu	Phe	Ala	Cys	Gly	Ser	Val	Trp	Pro
		35					40					45			

Gly	Ser	Leu	Gly	Ser	Gly	Ile	Phe	Ala	Arg	Leu	Ser	Gln	Leu	Leu	Pro
	50					55					60				

Ser	Pro	Ala	Ser	Trp	Gly	Trp	Asp	Phe	Leu	Thr	Leu	Arg	Gln	Ala	Gln
65					70					75					80

Gln	Met	Leu	Gly	Pro	Ser	Leu	Cys	Pro	Gly	His	Ser	Thr	Ser	Ala	His
				85					90						95

Gln His Tyr Gly Ala Tyr Val Leu Pro Arg Asp<sup>146</sup> Leu Cys Ser Phe Leu  
 100 105 110

Leu Thr Ser Thr Val Gln Gly Thr Ala Pro Leu Lys Asn Ser Arg Val  
 115 120 125

Thr Cys Leu Ile Gly Ser Gln Gln Val Pro Leu Cys  
 130 135 140

<210> 284

<211> 146

<212> PRT

<213> Homo sapiens

<400> 284

Ala Glu Val Thr Ser Pro Ala Lys Thr Asp Leu Gln Val Phe Val Ser  
 1 5 10 15

Arg Asp Leu Pro His Ala Arg Pro Leu Pro Leu Thr Ala Ala Pro Phe  
 20 25 30

Pro Leu Ile Val Pro Val Pro Phe Leu Pro Val Asp Leu Phe Gly Gln  
 35 40 45

Gly Pro Trp Gly Gln Glu Tyr Leu Gln Asp Ser Ala Ser Ser Phe Pro  
 50 55 60

Ala Gln Pro Leu Gly Ala Gly Thr Phe Ser Pro Cys Gly Arg His Asn  
 65 70 75 80

Arg Cys Trp Asp Pro Val Ser Ala Gln Val Thr Ala Gln Val His Ile  
 85 90 95

Ser Thr Met Gly Pro Met Ser Cys Pro Glu Thr Ser Ala Pro Ser Cys  
 100 105 110

Ser His Pro Gln Phe Arg Ala Arg Arg Pro Ser Arg Thr Pro Glu Ser  
 115 120 125

Pro Val Ser Ser Ala Pro Ser Lys Cys Leu Phe Val Tyr Asp Val Pro  
 130 135 140

Leu Leu  
 145

<210> 285

<211> 30

<212> PRT

<213> Homo sapiens

<400> 285

Ser Leu Arg Leu Lys Gly Pro Pro Ser Cys Gln Ala Pro Ala Ser His  
 1 5 10 15

Ser Ser Thr Leu Ser Ser His Cys Pro Cys Ser Leu Phe Ala  
 20 25 30

147

<210> 286  
<211> 30  
<212> PRT  
<213> Homo sapiens

<400> 286  
Gln Gln Met Leu Gly Pro Ser Leu Cys Pro Gly His Ser Thr Ser Ala  
1 5 10 15  
His Gln His Tyr Gly Ala Tyr Val Leu Pro Arg Asp Leu Cys  
20 25 30

<210> 287  
<211> 31  
<212> PRT  
<213> Homo sapiens

<400> 287  
Asp Leu Gln Val Phe Val Ser Arg Asp Leu Pro His Ala Arg Pro Leu  
1 5 10 15  
Pro Leu Thr Ala Ala Pro Phe Pro Leu Ile Val Pro Val Pro Phe  
20 25 30

<210> 288  
<211> 39  
<212> PRT  
<213> Homo sapiens

<400> 288  
Ala Gln Val His Ile Ser Thr Met Gly Pro Met Ser Cys Pro Glu Thr  
1 5 10 15  
Ser Ala Pro Ser Cys Ser His Pro Gln Phe Arg Ala Arg Arg Pro Ser  
20 25 30  
Arg Thr Pro Glu Ser Pro Val  
35

<210> 289  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 289  
Gln Ala Pro Pro Arg Gln Thr Cys Lys Ser Ser Ser Gln Gly Thr Ser  
1 5 10 15  
Leu

<210> 290

<211> 314  
 <212> PRT  
 <213> Homo sapiens

146

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (111)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 290

Ala Ala Leu Arg Pro Ser Gly Ser Leu Ala Gly Pro Glu Trp Pro Trp  
 1 5 10 15

Gln His Trp Cys Gly Cys Trp Arg Glu His Xaa Val Lys Pro Gln Gln  
 20 25 30

Val Asp Leu His Ser Ala Arg Leu Trp Ala Ala Pro Ala Ala Val Gly  
 35 40 45

Pro Ala His Ala Gly Gly Ser Pro Gly Met Pro Pro Gly Gly Thr Ala  
 50 55 60

Pro His Ala Arg Arg His Ser Leu Pro Ser Pro Thr Ala Gln Ser His  
 65 70 75 80

Leu Trp His Val His Gly Leu Arg Gln Arg Gly Pro Lys Ala Val Pro  
 85 90 95

Leu Asp Leu Ala Gln Leu Val Thr Thr Thr Thr Pro Leu Phe Xaa Leu  
 100 105 110

Ala Leu Ser Ala Leu Leu Leu Gly Arg Arg His His Pro Leu Gln Leu  
 115 120 125

Ala Ala Met Gly Pro Leu Cys Leu Gly Ala Ala Cys Ser Leu Ala Gly  
 130 135 140

Glu Phe Arg Thr Pro Pro Thr Gly Cys Gly Phe Leu Leu Ala Ala Thr  
 145 150 155 160

Cys Leu Arg Gly Leu Lys Ser Val Gln Gln Ser Ala Leu Leu Gln Glu  
 165 170 175

Glu Arg Leu Asp Ala Val Thr Leu Leu Tyr Ala Thr Ser Leu Pro Ser  
 180 185 190

Phe Cys Leu Leu Ala Gly Ala Ala Leu Val Leu Glu Ala Gly Val Ala  
 195 200 205

Pro Pro Pro Thr Ala Gly Asp Ser Arg Leu Trp Ala Cys Ile Leu Leu  
 210 215 220

Ser Cys Leu Leu Ser Val Leu Tyr Asn Leu Ala Ser Phe Ser Leu Leu

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<210> 291
<211> 66
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 291  
Gly Gln Pro Ser Gly Pro Pro Ala Ala Trp Pro Gly Pro Ser Gly His  
1 5 10 15

Gly Ser Thr Gly Val Ala Ala Gly Gly Ser Thr Xaa Ser Ser Leu Asn  
20 25 30

Lys Trp Ile Phe Thr Val His Gly Phe Gly Arg Pro Leu Leu Leu Ser  
35 40 45

Ala Leu His Met Leu Val Ala Ala Leu Ala Cys His Arg Gly Ala Arg  
50 55 60

Arg Pro  
65

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<210> 292
<211> 21
<212> PRT
<213> Homo sapiens
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<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 292  
Trp Pro Gly Pro Ser Gly His Gly Ser Thr Gly Val Ala Ala Gly Gly  
1 5 10 15

150

Ser Thr Xaa Ser Ser  
20

&lt;210&gt; 293

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 293

Glu Trp Pro Trp Gln His Trp Cys Gly Cys Trp Arg Glu His Xaa Val  
1 5 10 15

Lys Pro Gln Gln Val Asp Leu His Ser Ala  
20 25

&lt;210&gt; 294

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 294

Gln Gln Ser Ala Leu Leu Gln Glu Glu Arg Leu Asp Ala Val Thr Leu  
1 5 10 15

Leu Tyr Ala Thr Ser Leu Pro Ser Phe Cys Leu Leu  
20 25

&lt;210&gt; 295

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 295

Ala Cys Ile Leu Leu Ser Cys Leu Leu Ser Val Leu Tyr Asn Leu Ala  
1 5 10 15

Ser Phe Ser Leu Leu Ala Leu Thr Ser Ala Leu  
20 25

&lt;210&gt; 296

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 296

Ser Leu Asn Lys Trp Ile Phe Thr Val His Gly Phe Gly Arg Pro Leu  
1 5 10 15

Leu Leu Ser Ala Leu  
20

151

<210> 297  
<211> 17  
<212> PRT  
<213> Homo sapiens

<400> 297  
Lys Ser Thr Leu Ser Ala Ala Val Val Ala Thr Ile Leu Arg Thr Leu  
1 5 10 15

Ala

<210> 298  
<211> 100  
<212> PRT  
<213> Homo sapiens

<400> 298  
Gly Asp His Ser Glu Gln Cys Leu Ile Lys Glu Met Gly Ala Arg Glu  
1 5 10 15

Arg Arg Phe Cys Lys Ala Arg Gly Tyr Arg Asp Thr Gly Arg Glu Ala  
20 25 30

Gln Ala Lys Ala Gly Gly Arg Arg Gly Ser Gln Trp Asn Glu Ser Gln  
35 40 45

Cys Ser Ser Gln Arg Pro Arg Pro Ala Lys Glu Val Arg Lys Thr Arg  
50 55 60

Pro Arg Ala Gly Val Gly Arg Gly Pro Ala Leu Leu Gln Leu Ser Leu  
65 70 75 80

Leu Gln Gln Val Val Leu Tyr Val Arg Pro Ser Leu Arg Leu Val Trp  
85 90 95

Leu Lys Ala Ser  
100

<210> 299  
<211> 84  
<212> PRT  
<213> Homo sapiens

<400> 299  
Met Glu Arg Gly Glu Tyr Gly Gly Trp Gly Thr Tyr Gly Ser Leu Asp  
1 5 10 15

Leu Gly Ser Gln Leu Cys Thr Val Arg Ser Ser Gly Pro Cys Gly Ser  
20 25 30

Leu His Trp Gly Gln His Arg Ser Pro Ile Ser Gly Pro Asp Pro Asn

35 40 45  
Pro Ser Ser Ser Arg Gly Gln Gln Ser Ile Gly Ser Lys Val Gly Ser  
50 55 60  
Pro Ser Arg Ser Gln Trp Arg Ser Trp Lys Glu Val Gly Arg Asp Pro  
65 70 75 80  
Glu Lys Gly Glu

<210> 300  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 300  
Gln Ala Lys Ala Gly Gly Arg Arg Gly Ser Gln Trp Asn Glu Ser Gln  
1 5 10 15  
Cys Ser Ser Gln Arg Pro Arg  
20

<210> 301  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 301  
Val Gly Arg Gly Pro Ala Leu Leu Gln Leu Ser Leu Leu Gln Gln Val  
1 5 10 15  
Val Leu Tyr Val Arg Pro Ser Leu Arg Leu  
20 25

<210> 302  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 302  
Tyr Gly Ser Leu Asp Leu Gly Ser Gln Leu Cys Thr Val Arg Ser Ser  
1 5 10 15  
Gly Pro Cys Gly Ser Leu  
20

<210> 303  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 303  
Lys Val Gly Ser Pro Ser Arg Ser Gln Trp Arg Ser Trp Lys Glu Val

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1           5           10           15
Gly Arg Asp Pro
      20

<210> 304
<211> 214
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (18)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 304
Met Pro Gln Ser Leu Ser Ser Leu Ala Ser Ser Ser Ser Ser Phe Gln
 1           5           10           15

Arg Xaa Lys Pro Cys Phe Gly Lys Lys Asn Asp Gly Glu Asn Gln Glu
      20           25           30

His Ser Leu Gly Thr Glu Pro Ile Ile Thr Trp Lys Asp Phe Gln Lys
      35           40           45

Thr Met Pro Trp Glu Ile Val Ile Leu Val Gly Gly Gly Tyr Ala Leu
 50           55           60

Ala Ser Gly Ser Lys Ser Ser Gly Leu Ser Thr Trp Ile Gly Asn Gln
 65           70           75           80

Met Leu Ser Leu Ser Ser Leu Pro Pro Trp Ala Val Thr Leu Leu Ala
      85           90           95

Cys Ile Leu Val Ser Ile Val Thr Glu Phe Val Ser Asn Pro Ala Thr
      100          105          110

Ile Thr Ile Phe Leu Pro Ile Leu Cys Ser Leu Ser Glu Thr Leu His
      115          120          125

Ile Asn Pro Leu Tyr Thr Leu Ile Pro Val Thr Met Cys Ile Ser Phe
      130          135          140

Ala Val Met Leu Pro Val Gly Asn Pro Pro Asn Ala Ile Val Phe Ser
145          150          155          160

Tyr Gly His Cys Gln Ile Lys Asp Met Val Lys Ala Gly Leu Gly Val
      165          170          175

Asn Val Ile Gly Leu Val Ile Val Met Val Ala Ile Asn Thr Trp Gly
      180          185          190

Val Ser Leu Phe His Leu Asp Thr Tyr Pro Ala Trp Ala Arg Val Ser
      195          200          205

Asn Ile Thr Asp Gln Ala
      210

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154

<210> 305  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 305  
Asn Asp Gly Glu Asn Gln Glu His Ser Leu Gly Thr Glu Pro Ile Ile  
1 5 10 15  
Thr Trp Lys Asp Phe Gln Lys  
20

<210> 306  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 306  
Ile Gly Asn Gln Met Leu Ser Leu Ser Ser Leu Pro Pro Trp Ala Val  
1 5 10 15  
Thr Leu Leu Ala Cys Ile Leu Val  
20

<210> 307  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 307  
Ala Thr Ile Thr Ile Phe Leu Pro Ile Leu Cys Ser Leu Ser Glu Thr  
1 5 10 15  
Leu His Ile Asn Pro Leu Tyr Thr Leu Ile Pro  
20 25

<210> 308  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 308  
Leu Pro Val Gly Asn Pro Pro Asn Ala Ile Val Phe Ser Tyr Gly His  
1 5 10 15  
Cys Gln Ile Lys Asp Met Val Lys Ala Gly  
20 25

<210> 309  
<211> 29  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 309

155

Leu Val Ile Val Met Val Ala Ile Asn Thr Trp Gly Val Ser Leu Phe  
 1 5 10 15

His Leu Asp Thr Tyr Pro Ala Trp Ala Arg Val Ser Asn  
 20 25

&lt;210&gt; 310

&lt;211&gt; 133

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 310

Glu Thr Cys Pro Ser Asn Gly Ile Glu Leu Arg Gln Ala Pro Thr Ser  
 1 5 10 15

Leu Tyr Ile Leu Leu Leu His Ile Gln Pro Thr Pro Thr His Pro Met  
 20 25 30

Leu Gly Arg Ser Tyr Val Leu Pro Ala Phe Ser Xaa Asn Xaa Glu His  
 35 40 45

Gly Gly Leu Pro Asn Gln Ile Pro Lys Gly Asp Arg Asn Gly Asn Ile  
 50 55 60

Arg His Ser Arg Ile Thr Phe Pro Cys Ser Ser Ser Thr Leu Gln Pro  
 65 70 75 80

Glu Ser His Leu Gly Phe Ile Arg Ser Lys Leu His Gly Leu Val Arg  
 85 90 95

Pro Gly Lys Asp Leu Arg Gly Arg Arg Ser Leu Gln Leu Ser Lys His  
 100 105 110

Ser Leu Ser Thr Cys Tyr Met Leu Arg Trp Glu Thr Tyr Lys Gln Val  
 115 120 125

Ser Tyr Thr Ala Val  
 130

&lt;210&gt; 311

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 311

156

Gln Arg His Gln Glu Asn Asp Lys Arg Asn Val His Arg Phe Leu His  
 1 5 10 15

Thr Cys Val His Met Pro Met Cys Thr His Thr His Thr Gln Ala Val  
 20 25 30

Leu Ser Thr Trp Glu Gly Gln Phe Ser Asn Val Ala Ser Phe Thr Ser  
 35 40 45

Leu Lys Arg Ile Pro Leu Ser Ile Ile Tyr Ile His Ser Ser His Ser  
 50 55 60

Pro Arg Arg Phe Val Lys Val Cys Gln Leu Arg Gln Glu Lys Ala Leu  
 65 70 75 80

Glu Leu Thr Glu Val Tyr Val Ser Ala Ser Leu Lys Leu Gln Leu Tyr  
 85 90 95

His Leu His Cys His Phe His Thr Ala Val  
 100 105

&lt;210&gt; 312

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 312

Arg Gln Ala Pro Thr Ser Leu Tyr Ile Leu Leu Leu His Ile Gln Pro  
 1 5 10 15

Thr Pro Thr His Pro Met Leu Gly  
 20

&lt;210&gt; 313

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 313

Ser His Leu Gly Phe Ile Arg Ser Lys Leu His Gly Leu Val Arg Pro  
 1 5 10 15

Gly Lys Asp Leu Arg Gly Arg Arg Ser  
 20 25

&lt;210&gt; 314

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 314

Arg Asn Val His Arg Phe Leu His Thr Cys Val His Met Pro Met Cys  
 1 5 10 15

Thr His Thr His Thr Gln  
20

157

<210> 315  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 315  
Gln Leu Arg Gln Glu Lys Ala Leu Glu Leu Thr Glu Val Tyr Val Ser  
1 5 10 15

Ala Ser Leu Lys Leu Gln Leu Tyr His  
20 25

<210> 316  
<211> 31  
<212> PRT  
<213> Homo sapiens

<400> 316  
Pro Arg Val Arg Gly Arg Lys Glu Pro Gly Cys Leu Gly Pro Gly Arg  
1 5 10 15

Ala Gly Gly Asp Ser Gln Lys Glu Ile Gly Ser Trp Gln Gln Met  
20 25 30

<210> 317  
<211> 296  
<212> PRT  
<213> Homo sapiens

<400> 317  
Leu Ser Lys Gly Asn Arg Ile Met Ala Ala Asp Asp Asp Asn Gly Asp  
1 5 10 15

Gly Thr Ser Leu Phe Asp Val Phe Ser Ala Ser Pro Leu Lys Asn Asn  
20 25 30

Asp Glu Gly Ser Leu Asp Ile Tyr Ala Gly Leu Asp Ser Ala Val Ser  
35 40 45

Asp Ser Ala Ser Lys Ser Cys Val Pro Ser Arg Asn Cys Leu Asp Leu  
50 55 60

Tyr Glu Glu Ile Leu Thr Glu Glu Gly Thr Ala Lys Glu Ala Thr Tyr  
65 70 75 80

Asn Asp Leu Gln Val Glu Tyr Gly Lys Cys Gln Leu Gln Met Lys Glu  
85 90 95

Leu Met Lys Lys Phe Lys Glu Ile Gln Thr Gln Asn Phe Ser Leu Ile  
100 105 110

Asn Glu Asn Gln Ser Leu Lys Lys Asn Ile Ser Ala Leu Ile Lys Thr

115                      120              158              125  
 Ala Arg Val Glu Ile Asn Arg Lys Asp Glu Glu Ile Ser Asn Leu His  
     130                      135                      140  
 Gln Lys Ile Val Leu Ser Phe His Ile Phe Glu Ile Ile Ile Lys Leu  
     145                      150                      155                      160  
 Gln Gly His Leu Ile Gln Leu Lys Gln Lys Ile Leu Asn Leu Asp Leu  
                     165                      170                      175  
 His Ile Trp Met Ile Val Gln Arg Leu Ile Thr Arg Ala Lys Ser Asp  
                     180                      185                      190  
 Val Ser Lys Asp Val His His Ser Thr Ser Leu Pro Asn Leu Glu Lys  
                     195                      200                      205  
 Glu Gly Lys Pro His Ser Asp Lys Arg Ser Thr Ser His Leu Pro Thr  
                     210                      215                      220  
 Ser Val Glu Lys His Cys Thr Asn Gly Val Trp Ser Arg Ser His Tyr  
     225                      230                      235                      240  
 Gln Val Gly Glu Gly Ser Ser Asn Glu Asp Ser Arg Arg Gly Arg Lys  
                     245                      250                      255  
 Asp Ile Arg His Ser Gln Phe Asn Arg Gly Thr Glu Arg Val Arg Lys  
                     260                      265                      270  
 Asp Leu Ser Thr Gly Cys Gly Asp Gly Glu Pro Arg Ile Leu Glu Ala  
                     275                      280                      285  
 Ser Gln Arg Leu Gln Gly Thr Ser  
     290                      295

&lt;210&gt; 318

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 318

Asn Arg Ile Met Ala Ala Asp Asp Asp Asn Gly Asp Gly Thr Ser Leu  
     1                      5                      10                      15

Phe Asp Val Phe Ser Ala Ser Pro Leu Lys Asn  
                     20                      25

&lt;210&gt; 319

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 319

Cys Leu Asp Leu Tyr Glu Glu Ile Leu Thr Glu Glu Gly Thr Ala Lys  
     1                      5                      10                      15

Glu Ala Thr Tyr Asn Asp Leu  
20

159

<210> 320  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 320  
Asp Glu Glu Ile Ser Asn Leu His Gln Lys Ile Val Leu Ser Phe His  
1 5 10 15

Ile Phe Glu Ile Ile Ile Lys Leu Gln Gly  
20 25

<210> 321  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 321  
Glu Lys Glu Gly Lys Pro His Ser Asp Lys Arg Ser Thr Ser His Leu  
1 5 10 15

Pro Thr Ser Val Glu Lys  
20

<210> 322  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 322  
Thr Glu Arg Val Arg Lys Asp Leu Ser Thr Gly Cys Gly Asp Gly Glu  
1 5 10 15

Pro Arg Ile Leu Glu Ala Ser Gln Arg Leu  
20 25

<210> 323  
<211> 115  
<212> PRT  
<213> Homo sapiens

<400> 323  
Lys Ser Tyr Phe Arg Thr Met Gly Gly Thr Lys Arg Gly Ile Lys Lys  
1 5 10 15

Leu Val Asn Val Cys Leu Lys His Pro Lys Asn Thr Ser Leu Ser Gln  
20 25 30

Gln Leu Val Phe Ala Lys Ile Asn Lys Ile Leu Ile Ser Lys Thr Thr  
35 40 45

140

Lys Ser Thr Asn Leu Lys Gly Leu Lys Cys Leu Pro Pro Leu Ser Val  
 50 55 60  
 Ser Ile His Pro Thr Phe Ile Tyr Tyr Lys His Asn Thr Thr Leu Arg  
 65 70 75 80  
 Ile Val Phe Gly Thr Tyr Phe Asp Phe Phe Pro Tyr Arg Lys Asn Lys  
 85 90 95  
 Asp Gln Ala Phe Glu Gly Glu Asp Trp Glu Ser Ser Leu Asn Val Ser  
 100 105 110  
 Asp Ala Trp  
 115

&lt;210&gt; 324

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 324

Thr Lys Arg Gly Ile Lys Lys Leu Val Asn Val Cys Leu Lys His Pro  
 1 5 10 15

Lys Asn Thr Ser Leu Ser  
 20

&lt;210&gt; 325

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 325

Ser Ile His Pro Thr Phe Ile Tyr Tyr Lys His Asn Thr Thr Leu Arg  
 1 5 10 15

Ile Val Phe Gly Thr Tyr Phe Asp Phe Phe  
 20 25

&lt;210&gt; 326

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

161

&lt;222&gt; (45)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 326

Gln	Arg	Pro	His	Pro	Gln	Pro	Trp	Xaa	Pro	Met	Thr	Leu	Met	Gly	Thr
1				5					10					15	

Gly	Ile	Pro	Val	Phe	Ala	His	Lys	Met	Leu	Pro	Phe	Asp	Pro	Pro	Cys
			20					25					30		

His	Leu	Ser	Cys	Thr	His	Ile	Asn	Pro	Lys	Pro	Xaa	Xaa	Pro	Gln	Gly
		35					40					45			

Asp	Glu	Gln	Lys	Ser	Gln	Gly	Thr	Glu	Glu	Trp	Cys	Asp	Arg	Glu	Gly
	50					55					60				

Lys	Lys	Arg	Arg	Ser	Ile
65				70	

&lt;210&gt; 327

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

Pro	Met	Thr	Leu	Met	Gly	Thr	Gly	Ile	Pro	Val	Phe	Ala	His	Lys	Met
1				5					10					15	

Leu	Pro	Phe	Asp	Pro
			20	

&lt;210&gt; 328

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 328

Pro	Pro	Cys	His	Leu	Ser	Cys	Thr	His	Ile	Asn	Pro	Lys	Pro	Xaa	Xaa
1				5					10					15	

Pro	Gln	Gly	Asp	Glu
			20	

&lt;210&gt; 329

<211> 21  
 <212> PRT  
 <213> Homo sapiens

162

<400> 329  
 Glu Gln Lys Ser Gln Gly Thr Glu Glu Trp Cys Asp Arg Glu Gly Lys  
     1                    5                    10                    15  
 Lys Arg Arg Ser Ile  
                     20

<210> 330  
 <211> 70  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (64)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (65)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 330  
 Asp Glu Trp Gly Ala Gly Arg Arg Met Glu Trp Glu Asp Asn Leu Pro  
     1                    5                    10                    15  
 Leu Glu Phe Ser Cys Pro Val Thr Lys Leu Leu Ser Val Pro Ser Trp  
                     20                    25                    30  
 Thr Pro Leu Asp Ala Gln Met Leu Leu Leu Phe Phe Pro Ser Leu Ser  
                     35                    40                    45  
 His His Ser Ser Val Pro Trp Leu Phe Cys Ser Ser Pro Cys Gly Xaa  
     50                    55                    60  
 Xaa Gly Leu Gly Phe Ile  
     65                    70

<210> 331  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 331  
 Glu Trp Glu Asp Asn Leu Pro Leu Glu Phe Ser Cys Pro Val Thr Lys  
     1                    5                    10                    15  
 Leu Leu Ser Val Pro  
                     20

<210> 332

<211> 21  
 <212> PRT  
 <213> Homo sapiens

163

<400> 332  
 Pro Ser Trp Thr Pro Leu Asp Ala Gln Met Leu Leu Leu Phe Phe Pro  
       1                  5                  10                  15  
 Ser Leu Ser His His  
                   20

<210> 333  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 333  
 His Ser Ser Val Pro Trp Leu Phe Cys Ser Ser Pro Cys Gly Xaa Xaa  
       1                  5                  10                  15

Gly Leu Gly Phe Ile  
                   20

<210> 334  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 334  
 Gln Gly Leu Ser His Ile Phe Trp Met Asn Glu Gln Thr Leu Lys  
       1                  5                  10                  15

<210> 335  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 335  
 Thr Leu Val Cys Leu Gly Val Ser Ser Glu Glu Gly Ser Cys Pro Arg  
       1                  5                  10                  15

Asp Val Thr Gly Pro Gly Cys Cys Phe Ser Leu Thr Leu Thr Gly Phe  
                   20                  25                  30

164

<210> 336  
 <211> 233  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (78)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (79)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (80)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (231)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 336  
 Ala Asp Leu Ile Val Leu Trp His His His Pro Leu Trp Pro Gln His  
     1                    5                    10                    15

Leu Ala Leu Pro Ser Ser Gly Ala Ser His Asp His Val Glu Leu Thr  
                     20                    25                    30

Val Tyr Pro Lys Thr Val Ala Ala Ser Trp Leu Leu Glu Leu Ser Arg  
                     35                    40                    45

Pro Pro Ile Phe Cys Leu Phe Thr Xaa Pro Ala Leu Thr Xaa His Gly  
                     50                    55                    60

Leu Asp Arg Val Ala Ala Leu Val Glu Cys Thr Ile Trp Xaa Xaa Xaa  
     65                    70                    75                    80

Gly Met Trp Tyr Arg Arg Arg Tyr Ser Cys Cys Gln Phe Arg Asp Arg  
                     85                    90                    95

Ser Ile Arg Asp Val Phe Pro Glu Ala Val Met Leu Gln Gln His Leu

100 105 110  
 Arg His Leu Ala Val Ala Thr Tyr Arg Cys Arg Arg Arg Ser Pro Cys  
 115 120 125  
 Lys Ala Pro Thr Val Glu Glu Ala Glu Gly Gly Lys Pro Arg Ala Val  
 130 135 140  
 Pro Ser Gly Thr Gly Phe Gln Lys His Gly Gln Glu Pro Gly Gly Ser  
 145 150 155 160  
 Thr Ser Pro His Trp Phe Trp Gly His Leu Gln Leu Leu Val Leu Ser  
 165 170 175  
 Val Asn Asn Arg Gln Leu Phe Val Gln Gly Arg Ala Gly Tyr Leu Glu  
 180 185 190  
 Met Thr Gly Leu Pro Cys Pro Lys Leu Leu Leu Thr Leu Leu Arg Gly  
 195 200 205  
 Leu Thr Pro Gly Val Gly His Gly Leu Cys Ala Tyr Arg Arg Gly Cys  
 210 215 220  
 Leu Ala Trp Arg Leu Asp Xaa Ala Ser  
 225 230

&lt;210&gt; 337

&lt;211&gt; 176

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 337

Ile Leu Trp Arg Gln Ala Pro Glu Ala Pro His Cys Ser Gln Asp Ser  
 1 5 10 15

Val Ser Ser Ser Pro Arg Leu Gln Glu Asp Leu Ala His Val Thr Gln  
 20 25 30

Val Thr Arg His Pro His Phe Arg Ser Leu Pro Ser Ala Trp Cys Ser  
 35 40 45

His Ser Ser Leu Leu Pro Val Ser Leu Pro Arg His Ala Leu Ala Thr

50                      55                      60  
 Lys Ser Pro Asn Met Xaa Xaa Ser Ser Pro Ile Leu His Leu Ile Gln  
 65                      70                      75                      80  
 Phe Thr Gly Gln Ile Ser Ser Pro Leu Gly Gly Xaa Val Gln Pro Pro  
                          85                      90                      95  
 Gly Gln Thr Ala Ser Pro Ile Cys Thr Gln Pro Met Ser His Pro Arg  
                          100                      105                      110  
 Arg Gln Ala Ser Gln Gln Cys Glu Gln Gln Leu Trp Thr Gly Gln Thr  
                          115                      120                      125  
 Ser His Leu Gln Ile Pro Cys Pro Ala Leu Asn Lys Glu Leu Pro Val  
                          130                      135                      140  
 Val Asp Thr Gln Asp Lys Glu Leu Gln Met Ser Pro Glu Pro Met Trp  
 145                      150                      155                      160  
 Gly Cys Gly Pro Ser Arg Leu Leu Pro Met Leu Leu Glu Ser Cys Ala  
                          165                      170                      175

<210> 338  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 338  
 Met Leu Gln Gln His Leu Arg His Leu Ala Val Ala Thr Tyr Arg Cys  
   1                      5                      10                      15  
 Arg Arg Arg Ser Pro Cys Lys Ala Pro Thr Val Glu Glu Ala Glu Gly  
                          20                      25                      30  
 Gly Lys

<210> 339  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 339  
 Val Thr Gln Val Thr Arg His Pro His Phe Arg Ser Leu Pro Ser Ala  
   1                      5                      10                      15  
 Trp Cys Ser His Ser Ser Leu Leu Pro Val Ser Leu Pro  
                          20                      25

<210> 340  
 <211> 28

&lt;212&gt; PRT

167

&lt;213&gt; Homo sapiens

&lt;400&gt; 340

Gly Gln Thr Ala Ser Pro Ile Cys Thr Gln Pro Met Ser His Pro Arg  
 1 5 10 15

Arg Gln Ala Ser Gln Gln Cys Glu Gln Gln Leu Trp  
 20 25

&lt;210&gt; 341

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 341

Phe Ile Thr Leu Arg Leu Gly Pro Lys Asn Met Ala Gly Val Leu Trp  
 1 5 10 15

Arg His Ser Asn Leu Gln Thr Pro His Tyr Ile Ser Trp Cys Pro Leu  
 20 25 30

Leu Asn Tyr Arg Glu Thr Gly Asn Cys Leu Leu His Val Ser Gly Phe  
 35 40 45

Leu Asn Ser Arg Leu Leu Ala Asn Cys Ser Gly Glu Ala Ser Gly Lys  
 50 55 60

Val Ile Gln Thr Leu Leu Trp Pro Gly Glu Ile Ser Ala Val Ala  
 65 70 75

&lt;210&gt; 342

&lt;211&gt; 82

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 342

Lys Ile Arg Thr Phe Leu Phe Ser Gly His Arg Leu Phe Ser Thr Gln  
 1 5 10 15

Gly Gln Ser Leu Thr Val Lys Ala His Thr Ala Phe Met Leu Ile Val  
 20 25 30

Lys Asn Leu Arg Tyr Phe Ile Ala Phe Lys Phe Leu Met Gly Ile Ser  
 35 40 45

Asp Ser Ser Glu Ile Gly Leu Val Met Gln Pro Leu Gln Lys Pro His  
 50 55 60

Thr Val Ile Leu Ile Arg Gly Ile Glu Phe Leu Ser Pro Gly Gly Val  
 65 70 75 80

Leu Pro

<210> 343  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

168

<400> 343  
 Met Ala Gly Val Leu Trp Arg His Ser Asn Leu Gln Thr Pro His Tyr  
 1 5 10 15  
 Ile Ser Trp Cys Pro Leu Leu Asn Tyr Arg  
 20 25

<210> 344  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 344  
 Tyr Phe Ile Ala Phe Lys Phe Leu Met Gly Ile Ser Asp Ser Ser Glu  
 1 5 10 15  
 Ile Gly Leu Val Met Gln Pro Leu Gln Lys Pro His Thr  
 20 25

<210> 345  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 345  
 Asp Val Leu Leu Pro Leu Leu Tyr Leu Leu Val Arg Lys His Ile Asn  
 1 5 10 15  
 Arg Ala Gly Ile Gly Asn Thr Phe Gln Gly Gly Ala Asn Cys Ile  
 20 25 30

<210> 346  
 <211> 99  
 <212> PRT  
 <213> Homo sapiens

<400> 346  
 Met Cys Cys Cys Leu Cys Cys Thr Ser Trp Ser Gly Ser Thr Ser Thr  
 1 5 10 15  
 Glu Arg Val Ser Gly Thr Arg Phe Arg Glu Val Pro Thr Ala Ser Cys  
 20 25 30  
 Ser Ser Ser Ala Pro Ala Pro Ser Glu Leu Gly Ser Ser Leu Ser Val  
 35 40 45  
 Ala Ala Ala Ala Leu Leu Ser Leu Pro Pro Arg Ala Arg Leu Ala Leu  
 50 55 60  
 Pro Arg Leu Pro Arg Leu Pro Ser Gln Glu Asn Leu Arg Asn Pro Lys

Leu Pro Pro Arg Ser Ser Gly Ser Lys Phe Xaa Arg Tyr Gln Arg Pro

Thr Arg Ser Val Asp Val Leu Pro Asp Gln Glu Val Gln Gln Arg Gln  
130 135 140

Gln His Ile  
145

(7)

<210> 349  
<211> 31  
<212> PRT  
<213> Homo sapiens

<400> 349  
Arg Arg Ile Ser Gly Ile Pro Arg Asp Pro Arg Gly Thr Ser Lys His  
1 5 10 15

Leu Glu Leu Leu Ser Phe Leu Val Leu Trp His Arg Cys Cys Leu  
20 25 30

<210> 350  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 350  
Arg Thr Lys Ala Pro Gly Ala Trp Lys Phe Pro Trp Gly Pro Leu Gly  
1 5 10 15

Phe Leu Arg Phe Ser Trp Leu Gly Arg Arg Gly Ser Leu  
20 25

<210> 351  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 351  
Pro Arg Leu Ala Gln Leu Arg Leu Leu Ser Leu  
1 5 10

<210> 352  
<211> 178  
<212> PRT  
<213> Homo sapiens

<400> 352  
Gln Ser Asp Phe Arg Glu Met Asn Gln Thr Asn Ser Thr Ser Asn Ala  
1 5 10 15

Ala Lys Ala Arg Glu Ala Gln Gln Gly Arg Gly Arg Asp Arg Glu Ala  
20 25 30

Ile Phe Ser Ser Ser Ala Leu Glu His Leu Val Cys Tyr Leu Gln Ala  
35 40 45

Tyr Lys His Thr Leu Leu Phe Ile Arg Ser Leu Asn Glu His Gly Leu  
50 55 60

172

Gln	Gln	Leu	Leu	Phe	Gln	Trp	Arg	Asp	Gly	Leu	Phe	Gly	Asn	Trp	Tyr
65					70					75					80
Phe	Arg	Ile	Pro	Ile	Leu	Leu	Phe	Phe	Thr	Gly	Phe	His	Cys	Tyr	His
				85					90					95	
Leu	Ser	Cys	Pro	His	Leu	Pro	Cys	Ala	Gln	Arg	Gln	Ser	Ser	Arg	Gly
			100					105						110	
Thr	Val	Pro	Tyr	Val	Leu	Cys	Pro	His	Pro	His	His	His	Leu	His	His
		115					120					125			
Tyr	Ser	Trp	Phe	Pro	Phe	Leu	Ile	Pro	Val	Leu	His	Thr	Leu	Pro	Lys
	130					135					140				
Leu	Gln	Pro	Lys	Phe	His	Gly	Arg	Pro	Glu	Gln	Pro	Leu	Asn	Leu	Leu
145					150					155					160
Gln	Val	Lys	Pro	Thr	Ser	Gly	Thr	Ile	Ala	Ser	Ala	Glu	Gln	Val	Trp
				165					170					175	

Val Lys

<210> 353  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 353  
 Val Cys Tyr Leu Gln Ala Tyr Lys His Thr Leu Leu Phe Ile Arg Ser  
 1 5 10 15  
 Leu Asn Glu His Gly Leu Gln Gln Leu Leu Phe Gln Trp  
 20 25

<210> 354  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 354  
 Val Pro Tyr Val Leu Cys Pro His Pro His His His Leu His His Tyr  
 1 5 10 15  
 Ser Trp Phe Pro Phe Leu Ile Pro Val Leu His Thr Leu Pro Lys Leu  
 20 25 30

<210> 355  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

(73)

&lt;400&gt; 355

Glu Ser Glu Arg Ala Val Val Tyr Leu Ile Thr Gly Ala Leu Phe Ile  
 1 5 10 15

Val Ser Ser Cys Val Leu Cys Phe Leu Pro Ser Ser Arg Arg Glu  
 20 25 30

&lt;210&gt; 356

&lt;211&gt; 249

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (221)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 356

Met Trp Val Xaa Gly Glu Glu Val Leu Gly Ser His Ala Ala Ser Pro  
 1 5 10 15

Ala Phe Leu His Arg Cys Phe Ser Glu Glu Ser Cys Val Ser Ile Pro  
 20 25 30

Glu Val Glu Gly Tyr Val Val Val Leu Gln Pro Asp Ala Pro Gln Ile  
 35 40 45

Leu Leu Ser Gly Thr Ala His Phe Ala Arg Pro Ala Val Asp Phe Glu  
 50 55 60

Gly Thr Asn Gly Val Pro Leu Phe Pro Asp Leu Gln Ile Thr Cys Ser  
 65 70 75 80

Ile Ser His Gln Val Glu Ala Lys Lys Asp Glu Ser Trp Gln Gly Thr  
 85 90 95

Val Thr Asp Thr Arg Met Ser Asp Glu Ile Val His Asn Leu Asp Gly  
 100 105 110

Cys Glu Ile Ser Leu Val Gly Asp Asp Leu Asp Pro Glu Arg Glu Ser  
 115 120 125

Leu Leu Leu Asp Thr Thr Ser Leu Gln Gln Arg Gly Leu Glu Leu Thr  
 130 135 140

Asn Thr Ser Ala Tyr Leu Thr Ile Ala Gly Val Glu Ser Ile Thr Val  
 145 150 155 160

Tyr Glu Glu Ile Leu Arg Gln Ala Arg Tyr Arg Leu Arg His Gly Ala  
 165 170 175

(74)

Ala Leu Tyr Thr Arg Lys Phe Arg Leu Ser Cys Ser Glu Met Asn Gly  
 180 185 190

Arg Tyr Ser Ser Asn Glu Phe Ile Val Glu Val Asn Val Leu His Ser  
 195 200 205

Met Asn Arg Val Ala His Pro Ser His Val Leu Ser Xaa Gln Gln Phe  
 210 215 220

Leu His Arg Gly His Gln Pro Pro Pro Glu Met Ala Gly His Ser Leu  
 225 230 235 240

Ala Ser Ser His Arg Asn Ser Ser Thr  
 245

<210> 357  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 357  
 Leu Gly Ser His Ala Ala Ser Pro Ala Phe Leu His Arg Cys Phe Ser  
 1 5 10 15

Glu Glu Ser Cys Val Ser Ile  
 20

<210> 358  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 358  
 Gly Tyr Val Val Val Leu Gln Pro Asp Ala Pro Gln Ile Leu Leu Ser  
 1 5 10 15

Gly Thr Ala His Phe Ala Arg Pro Ala Val Asp Phe Glu  
 20 25

<210> 359  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 359  
 Ile Thr Cys Ser Ile Ser His Gln Val Glu Ala Lys Lys Asp Glu Ser  
 1 5 10 15

Trp Gln Gly Thr Val Thr Asp Thr Arg Met  
 20 25

<210> 360  
 <211> 29  
 <212> PRT

&lt;213&gt; Homo sapiens

175

&lt;400&gt; 360

Asn Leu Asp Gly Cys Glu Ile Ser Leu Val Gly Asp Asp Leu Asp Pro  
1 5 10 15

Glu Arg Glu Ser Leu Leu Leu Asp Thr Thr Ser Leu Gln  
20 25

&lt;210&gt; 361

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 361

Ser Ala Tyr Leu Thr Ile Ala Gly Val Glu Ser Ile Thr Val Tyr Glu  
1 5 10 15

Glu Ile Leu Arg Gln Ala Arg  
20

&lt;210&gt; 362

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 362

Arg Leu Ser Cys Ser Glu Met Asn Gly Arg Tyr Ser Ser Asn Glu Phe  
1 5 10 15

Ile Val Glu Val Asn Val Leu His Ser Met  
20 25

&lt;210&gt; 363

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 363

Gln Gln Phe Leu His Arg Gly His Gln Pro Pro Pro Glu Met Ala Gly  
1 5 10 15

His Ser Leu Ala Ser Ser His Arg Asn  
20 25

&lt;210&gt; 364

&lt;211&gt; 299

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (52)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

176

&lt;400&gt; 364

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Met Ala Asp Ser Glu Thr Phe Ile Ser Leu Glu Glu Cys Arg Gly His
 1           5           10          15

Lys Arg Ala Arg Lys Arg Thr Ser Met Glu Thr Ala Leu Ala Leu Glu
          20           25           30

Lys Leu Phe Pro Lys Gln Cys Gln Val Leu Gly Ile Val Thr Pro Gly
          35           40           45

Ile Val Val Xaa Pro Met Gly Ser Gly Ser Asn Arg Pro Gln Glu Ile
          50           55           60

Glu Ile Gly Glu Ser Gly Phe Ala Leu Leu Phe Pro Gln Ile Glu Gly
          65           70           75           80

Ile Lys Ile Gln Pro Phe His Phe Ile Lys Asp Pro Lys Asn Leu Thr
          85           90           95

Leu Glu Arg His Gln Leu Thr Glu Val Gly Leu Leu Asp Asn Pro Glu
          100          105          110

Leu Arg Val Val Leu Val Phe Gly Tyr Asn Cys Cys Lys Val Gly Ala
          115          120          125

Ser Asn Tyr Leu Gln Gln Val Val Ser Thr Phe Ser Asp Met Asn Ile
          130          135          140

Ile Leu Ala Gly Gly Gln Val Asp Asn Leu Ser Ser Leu Thr Ser Glu
          145          150          155          160

Lys Asn Pro Leu Asp Ile Asp Ala Ser Gly Val Val Gly Leu Ser Phe
          165          170          175

Ser Gly His Arg Ile Gln Ser Ala Thr Val Leu Leu Asn Glu Asp Val
          180          185          190

Ser Asp Glu Lys Thr Ala Glu Ala Ala Met Gln Arg Leu Lys Ala Ala
          195          200          205

Asn Ile Pro Glu His Asn Thr Ile Gly Phe Met Phe Ala Cys Val Gly
          210          215          220

Arg Gly Phe Gln Tyr Tyr Arg Ala Lys Gly Asn Val Glu Ala Asp Ala
          225          230          235          240

Phe Arg Lys Phe Phe Pro Ser Val Pro Leu Phe Gly Phe Phe Gly Asn
          245          250          255

Gly Glu Ile Gly Cys Asp Arg Ile Val Thr Gly Asn Phe Ile Leu Arg
          260          265          270

Lys Cys Asn Glu Val Lys Asp Asp Asp Leu Phe His Ser Tyr Thr Thr
          275          280          285

Ile Met Ala Leu Ile His Leu Gly Ser Ser Lys
          290          295

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177

<210> 365  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 365  
His Lys Arg Ala Arg Lys Arg Thr Ser Met Glu Thr Ala Leu Ala Leu  
1 5 10 15  
Glu Lys Leu Phe Pro  
20

<210> 366  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 366  
Met Gly Ser Gly Ser Asn Arg Pro Gln Glu Ile Glu Ile Gly Glu Ser  
1 5 10 15  
Gly Phe Ala Leu Leu Phe Pro Gln  
20

<210> 367  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 367  
Phe His Phe Ile Lys Asp Pro Lys Asn Leu Thr Leu Glu Arg His Gln  
1 5 10 15  
Leu Thr Glu Val Gly Leu  
20

<210> 368  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 368  
Phe Gly Tyr Asn Cys Cys Lys Val Gly Ala Ser Asn Tyr Leu Gln Gln  
1 5 10 15  
Val Val Ser Thr Phe Ser Asp  
20

<210> 369  
<211> 20  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 369

178

Thr Ser Glu Lys Asn Pro Leu Asp Ile Asp Ala Ser Gly Val Val Gly  
1 5 10 15

Leu Ser Phe Ser  
20

&lt;210&gt; 370

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 370

Asn Glu Asp Val Ser Asp Glu Lys Thr Ala Glu Ala Ala Met Gln Arg  
1 5 10 15

Leu Lys Ala Ala Asn Ile Pro Glu His Asn  
20 25

&lt;210&gt; 371

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 371

Tyr Tyr Arg Ala Lys Gly Asn Val Glu Ala Asp Ala Phe Arg Lys Phe  
1 5 10 15

Phe Pro Ser Val Pro Leu Phe Gly Phe  
20 25

&lt;210&gt; 372

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 372

Ile Gly Cys Asp Arg Ile Val Thr Gly Asn Phe Ile Leu Arg Lys Cys  
1 5 10 15

Asn Glu Val Lys Asp Asp Asp Leu Phe His  
20 25

&lt;210&gt; 373

&lt;211&gt; 341

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 373

Met Pro Lys Arg Lys Val Thr Phe Gln Gly Val Gly Asp Glu Glu Asp  
1 5 10 15

Glu Asp Glu Ile Ile Val Pro Lys Lys Lys Leu Val Asp Pro Val Ala

20										25				30			
Gly	Ser	Gly	Gly	Pro	Gly	Ser	Arg	Phe	Lys	Gly	Lys	His	Ser	Leu	Asp		
		35				40						45					
Ser	Asp	Glu	Glu	Glu	Asp	Asp	Asp	Asp	Gly	Gly	Ser	Ser	Lys	Tyr	Asp		
		50				55				60							
Ile	Leu	Ala	Ser	Glu	Asp	Val	Glu	Gly	Gln	Glu	Ala	Ala	Thr	Leu	Pro		
65				70						75				80			
Ser	Glu	Gly	Gly	Val	Arg	Ile	Thr	Pro	Phe	Asn	Leu	Gln	Glu	Glu	Met		
				85				90						95			
Glu	Glu	Gly	His	Phe	Asp	Ala	Asp	Gly	Asn	Tyr	Phe	Leu	Asn	Arg	Asp		
		100						105				110					
Ala	Gln	Ile	Arg	Asp	Ser	Trp	Leu	Asp	Asn	Ile	Asp	Trp	Val	Lys	Ile		
		115				120						125					
Arg	Glu	Arg	Pro	Pro	Gly	Gln	Arg	Gln	Ala	Ser	Asp	Ser	Glu	Glu	Glu		
130						135				140							
Asp	Ser	Leu	Gly	Gln	Thr	Ser	Met	Ser	Ala	Gln	Ala	Leu	Leu	Glu	Gly		
145				150						155				160			
Leu	Leu	Glu	Leu	Leu	Leu	Pro	Arg	Glu	Thr	Val	Ala	Gly	Ala	Leu	Arg		
				165				170						175			
Arg	Leu	Gly	Ala	Arg	Gly	Gly	Gly	Lys	Gly	Arg	Lys	Gly	Pro	Gly	Gln		
		180						185				190					
Pro	Ser	Ser	Pro	Gln	Arg	Leu	Asp	Arg	Leu	Ser	Gly	Leu	Ala	Asp	Gln		
		195				200						205					
Met	Val	Ala	Arg	Gly	Asn	Leu	Gly	Val	Tyr	Gln	Glu	Thr	Arg	Glu	Arg		
210						215				220							
Leu	Ala	Met	Arg	Leu	Lys	Gly	Leu	Gly	Cys	Gln	Thr	Leu	Gly	Pro	His		
225				230						235				240			
Asn	Pro	Thr	Pro	Pro	Pro	Ser	Leu	Asp	Met	Phe	Ala	Glu	Glu	Leu	Ala		
				245				250						255			
Glu	Glu	Glu	Leu	Glu	Thr	Pro	Thr	Pro	Thr	Gln	Arg	Gly	Glu	Ala	Glu		
		260						265				270					
Ser	Arg	Gly	Asp	Gly	Leu	Val	Asp	Val	Met	Trp	Glu	Tyr	Lys	Trp	Glu		
		275				280				285							
Asn	Thr	Gly	Asp	Ala	Glu	Leu	Tyr	Gly	Pro	Phe	Thr	Ser	Ala	Gln	Met		
290						295				300							
Gln	Thr	Trp	Val	Ser	Glu	Gly	Tyr	Phe	Pro	Asp	Gly	Val	Tyr	Cys	Arg		
305				310						315				320			
Lys	Leu	Asp	Pro	Pro	Gly	Gly	Gln	Phe	Tyr	Asn	Ser	Lys	Arg	Ile	Asp		
				325				330						335			

180

Phe Asp Leu Tyr Thr  
340

<210> 374  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 374  
Thr Phe Gln Gly Val Gly Asp Glu Glu Asp Glu Asp Glu Ile Ile Val  
1 5 10 15

Pro Lys Lys Lys Leu Val Asp Pro  
20

<210> 375  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 375  
Pro Gly Ser Arg Phe Lys Gly Lys His Ser Leu Asp Ser Asp Glu Glu  
1 5 10 15

Glu Asp Asp Asp Asp Gly Gly Ser Ser Lys Tyr  
20 25

<210> 376  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 376  
Glu Ala Ala Thr Leu Pro Ser Glu Gly Gly Val Arg Ile Thr Pro Phe  
1 5 10 15

Asn Leu Gln Glu Glu Met Glu Glu Gly  
20 25

<210> 377  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 377  
Phe Leu Asn Arg Asp Ala Gln Ile Arg Asp Ser Trp Leu Asp Asn Ile  
1 5 10 15

Asp Trp Val Lys Ile Arg Glu Arg Pro Pro Gly Gln Arg  
20 25

<210> 378

<211> 26  
<212> PRT  
<213> Homo sapiens

181

<400> 378  
Ser Leu Gly Gln Thr Ser Met Ser Ala Gln Ala Leu Leu Glu Gly Leu  
1 5 10 15  
Leu Glu Leu Leu Leu Pro Arg Glu Thr Val  
20 25

<210> 379  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 379  
Arg Gly Gly Gly Lys Gly Arg Lys Gly Pro Gly Gln Pro Ser Ser Pro  
1 5 10 15  
Gln Arg Leu Asp Arg Leu Ser Gly Leu Ala Asp Gln  
20 25

<210> 380  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 380  
Gln Glu Thr Arg Glu Arg Leu Ala Met Arg Leu Lys Gly Leu Gly Cys  
1 5 10 15  
Gln Thr Leu Gly Pro His Asn Pro  
20

<210> 381  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 381  
Asp Met Phe Ala Glu Glu Leu Ala Glu Glu Glu Leu Glu Thr Pro Thr  
1 5 10 15  
Pro Thr Gln Arg Gly Glu Ala Glu Ser Arg Gly Asp  
20 25

<210> 382  
<211> 30  
<212> PRT  
<213> Homo sapiens

<400> 382  
Glu Leu Tyr Gly Pro Phe Thr Ser Ala Gln Met Gln Thr Trp Val Ser

1				5						10					15
Glu	Gly	Tyr	Phe	Pro	Asp	Gly	Val	Tyr	Cys	Arg	Lys	Leu	Asp		
			20					25					30		
<210> 383															
<211> 14															
<212> PRT															
<213> Homo sapiens															
<400> 383															
Pro	His	Ser	Ser	Arg	Val	Ser	Phe	Leu	Gln	Ser	Leu	Ser	Phe		
1				5					10						
<210> 384															
<211> 141															
<212> PRT															
<213> Homo sapiens															
<400> 384															
Arg	Gly	Gln	Pro	Arg	Pro	Cys	Val	Ser	Gly	Val	Cys	Leu	Ser	Pro	His
1				5					10					15	
Ser	Arg	Phe	Trp	Glu	Cys	Cys	Ser	Phe	Tyr	Leu	Gln	Gly	Leu	Pro	Ala
			20					25					30		
Leu	Arg	Cys	Ser	Arg	Thr	Pro	Pro	Gly	Cys	His	Phe	Phe	Arg	Val	Phe
		35					40					45			
Pro	Ser	Cys	Pro	Phe	Ser	Ser	Ser	Arg	Ser	Pro	Ser	Cys	Phe	Thr	His
	50					55					60				
Ile	Cys	Pro	Val	Val	Arg	Ile	Gln	Phe	Ser	Arg	Ala	Leu	Trp	Val	Ser
65					70					75					80
Thr	Cys	Leu	Val	Leu	Ala	Ile	Thr	Pro	Gly	Lys	Trp	Leu	Leu	Pro	Glu
				85					90					95	
Asp	Arg	Ala	Leu	Ser	Leu	Met	Leu	Leu	Ala	Ser	Leu	Gln	Cys	Cys	Pro
			100					105					110		
Pro	Pro	Phe	Gly	Ala	Trp	Trp	Met	Gln	Val	Leu	Thr	His	Lys	Gly	Arg
		115					120					125			
Gln	Ala	Gly	Leu	Gly	Pro	Gly	Val	Ser	Ser	Arg	Pro	Leu			
	130					135					140				
<210> 385															
<211> 133															
<212> PRT															
<213> Homo sapiens															
<400> 385															
Ser	Asn	Ile	Lys	Ser	Leu	Pro	Pro	Thr	Asn	Ser	Leu	Ser	Leu	Leu	Arg
1				5					10					15	

123

Ala Gln Thr Gly Thr Asp Cys Ala Val Ser Pro Gly Leu Ala Gly Pro  
                   20                  25                  30

Cys His Gln Arg Gly Leu Glu Asp Thr Pro Gly Pro Arg Pro Ala Cys  
                   35                  40                  45

Leu Pro Leu Cys Val Ser Thr Cys Ile His Gln Ala Pro Lys Gly Gly  
           50                  55                  60

Gly Gln His Trp Arg Glu Ala Ser Ser Ile Arg Asp Arg Ala Leu Ser  
       65                  70                  75                  80

Ser Gly Arg Ser His Phe Pro Gly Val Met Ala Lys Thr Lys His Val  
                   85                  90                  95

Asp Thr His Asn Ala Arg Glu Asn Trp Ile Arg Thr Thr Gly Gln Met  
                   100                  105                  110

Trp Val Lys His Glu Gly Glu Arg Glu Glu Glu Lys Gly His Glu Gly  
           115                  120                  125

Lys Thr Leu Lys Lys  
       130

&lt;210&gt; 386

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 386

Val Cys Leu Ser Pro His Ser Arg Phe Trp Glu Cys Cys Ser Phe Tyr  
       1                  5                  10                  15

Leu Gln Gly Leu Pro Ala Leu Arg Cys  
           20                  25

&lt;210&gt; 387

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 387

Gln Phe Ser Arg Ala Leu Trp Val Ser Thr Cys Leu Val Leu Ala Ile  
       1                  5                  10                  15

Thr Pro Gly Lys Trp Leu Leu Pro Glu Asp Arg  
           20                  25

&lt;210&gt; 388

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

184

Ser	Leu	Ser	Leu	Leu	Arg	Ala	Gln	Thr	Gly	Thr	Asp	Cys	Ala	Val	Ser
1				5					10					15	

Pro	Gly	Leu	Ala	Gly	Pro	Cys	His	Gln	Arg	Gly
			20					25		

<210> 389  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 389

Ser	Gly	Arg	Ser	His	Phe	Pro	Gly	Val	Met	Ala	Lys	Thr	Lys	His	Val
1				5					10					15	

Asp	Thr	His	Asn	Ala	Arg	Glu	Asn	Trp	Ile	Arg	Thr
			20					25			

<210> 390  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 390

Ala	Arg	Val	Glu	Val	Gln	Gly	Gln	Gly	Pro	Gly	Ala	Lys	Val	Asp	Ala
1				5					10					15	

Gly	Glu	Gly	Gln
			20

<210> 391  
<211> 121  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (46)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (66)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (98)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (121)  
<223> Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 391

185

Trp Val Val Leu Ser Gln Leu Gln Ala Gln Gly Val Ala Gly Met Met  
 1 5 10 15

Cys Ser Tyr Pro Glu Gly Gln Lys Lys Gly Lys Glu Ala Thr Arg Ser  
 20 25 30

His Arg Trp Val Pro Arg Ser Leu Pro Gly Met Gly Ser Xaa Leu Ala  
 35 40 45

Ala Pro His Ser Asn Pro Trp Leu Ala Pro Leu Ala Leu Leu Glu Ile  
 50 55 60

Pro Xaa Pro Val Leu Cys Glu Trp Lys Arg Lys Leu Ile Ala Leu Glu  
 65 70 75 80

Glu Val Ser Glu Cys Arg Pro Gly Val Gly Gly Gly Gly Gly Phe Leu  
 85 90 95

Ser Xaa Cys Arg Arg Gly His Leu Ser Phe Leu Ser Gly Ala Pro Tyr  
 100 105 110

Pro Leu Phe Pro Ile Ser Pro Leu Xaa  
 115 120

&lt;210&gt; 392

&lt;211&gt; 206

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (105)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (127)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (131)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (180)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 392

Glu Leu Arg His Gly Gly Pro Arg Gln Val Lys Asp Ser Phe Leu Asp  
 1 5 10 15

Tyr Met Gly Tyr Pro Asp Glu Asp Arg Ala Gly Pro Pro Ser Arg Trp  
 20 25 30

186

Phe Pro Arg Glu Arg Phe Leu Ser Pro Pro Thr Val Val Pro Leu Cys  
                   35                                  40                                  45  
 Val Glu Leu Arg Leu Gly Phe Glu Ser Gly Met Gly Trp Gly Val Pro  
                   50                                  55                                  60  
 Gly Ser Ser His Ser Glu Gly Gly Pro Glu Ala Arg Trp Pro Leu Ile  
                   65                                  70                                  75                                  80  
 Ala Pro Met Tyr Thr Val Thr Gln Trp Phe Gln Arg Pro Asn Ser Gly  
                                   85                                  90                                  95  
 Arg Gly Pro Gln Pro Pro Pro Gln Xaa Arg Gly Glu Ile Gly Lys Arg  
                                   100                                  105                                  110  
 Gly Tyr Gly Ala Pro Glu Arg Lys Leu Arg Trp Pro Leu Leu Xaa Trp  
                   115                                  120                                  125  
 Glu Arg Xaa Pro Pro Pro Pro Pro Thr Pro Gly Arg His Ser Glu Thr  
                   130                                  135                                  140  
 Ser Ser Ser Ala Ile Ser Phe Leu Phe His Ser Gln Arg Thr Gly Trp  
                   145                                  150                                  155                                  160  
 Gly Ile Ser Ser Ser Ala Asn Gly Ala Ser Gln Gly Leu Leu Trp Gly  
                                   165                                  170                                  175  
 Ala Ala Arg Xaa Leu Pro Ile Pro Gly Arg Asp Leu Gly Thr His Leu  
                                   180                                  185                                  190  
 Trp Asp Leu Val Ala Ser Phe Pro Phe Phe Cys Pro Ser Gly  
                   195                                  200                                  205

&lt;210&gt; 393

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 393

Pro Glu Gly Gln Lys Lys Gly Lys Glu Ala Thr Arg Ser His Arg Trp  
           1                                  5                                  10                                  15

Val Pro Arg Ser Leu Pro Gly Met  
                                   20

&lt;210&gt; 394

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 394

Leu Arg Leu Gly Phe Glu Ser Gly Met Gly Trp Gly Val Pro Gly Ser  
           1                                  5                                  10                                  15

Ser His Ser Glu Gly Gly Pro Glu Ala Arg  
                   20                                  25

187

<210> 395  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 395  
His Ser Gln Arg Thr Gly Trp Gly Ile Ser Ser Ser Ala Asn Gly Ala  
1 5 10 15  
Ser Gln Gly Leu Leu Trp Gly Ala  
20

<210> 396  
<211> 54  
<212> PRT  
<213> Homo sapiens

<400> 396  
Phe Ile Met Lys Leu Leu Tyr Gln Leu Leu Met Leu Thr Thr Ser Ser  
1 5 10 15  
Ser Tyr Ser Leu Ile Thr His Leu Cys Tyr Ser Ile Phe Leu Cys Ser  
20 25 30  
Phe Tyr Phe His Phe Pro Cys Asn Val Ser Leu Phe Val Leu Ile Ser  
35 40 45  
Glu Glu Phe Ile Tyr Asp  
50

<210> 397  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 397  
Leu Met Leu Thr Thr Ser Ser Ser Tyr Ser Leu Ile Thr His Leu Cys  
1 5 10 15  
Tyr Ser Ile Phe Leu  
20

<210> 398  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 398  
Leu Cys Ser Phe Tyr Phe His Phe Pro Cys Asn Val Ser Leu Phe Val  
1 5 10 15  
Leu Ile Ser Glu Glu  
20

188

&lt;210&gt; 399

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 399

Met Arg Lys Asn Ile Phe Ala Ile Leu Asp Lys Met Leu Thr Cys Leu  
1 5 10 15

Ile Ile Asn Glu Leu Phe Arg Asn Gln Tyr Lys Glu Thr Asn Ile Thr  
20 25 30

Arg Glu Val Lys Ile Lys Gly Thr Glu Glu Asn Gly Ile Ala Gln Met  
35 40 45

Ser Tyr Lys Ala Ile  
50

&lt;210&gt; 400

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 400

Asp Lys Met Leu Thr Cys Leu Ile Ile Asn Glu Leu Phe Arg Asn Gln  
1 5 10 15

Tyr Lys Glu Thr Asn  
20

&lt;210&gt; 401

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 401

Asn Ile Thr Arg Glu Val Lys Ile Lys Gly Thr Glu Glu Asn Gly Ile  
1 5 10 15

Ala Gln Met Ser Tyr  
20

&lt;210&gt; 402

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 402

Gly Ile Ser Glu Arg Lys Pro  
1 5

&lt;210&gt; 403

<211> 25  
 <212> PRT  
 <213> Homo sapiens

189

<400> 403  
 Gln Ser Pro Ala Val Ser Tyr Thr Val Thr Ser Gln Val Pro Trp Gly  
 1 5 10 15  
 Leu Gly Leu Leu Ala Gly Glu Lys Arg  
 20 25

<210> 404  
 <211> 100  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (96)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 404  
 Leu Pro Ser His Pro Leu Arg Pro Leu Thr Phe Ser Ser Ala Met Cys  
 1 5 10 15  
 Met His Leu Pro Pro Pro Leu Cys Arg Arg Ala Ala Leu Ser Ala Pro  
 20 25 30  
 Phe Ala Thr Gln His Arg Pro Trp Ser Val Ala Ala Ala Cys Leu Pro  
 35 40 45  
 Arg Ile His Gln Asn Pro Leu Asp Ala Glu Tyr Pro Ser Gly Cys Cys  
 50 55 60  
 Arg Met Ser Phe Leu Pro Ala Ala Cys Ser Asn Ile Tyr Ser Gln Glu  
 65 70 75 80  
 Cys His Tyr Thr Leu Met Ser His Ser Glu Ala Ser Thr Leu Gln Xaa  
 85 90 95  
 Ala Gln Leu Leu  
 100

<210> 405  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 405  
 Met Leu Leu Gln Ala Ala Gly Arg Lys Leu Met Arg Gln Gln Pro Asp  
 1 5 10 15  
 Gly Tyr Ser Ala Ser Arg Gly Phe Trp Trp Met Arg Gly Arg Gln Ala  
 20 25 30  
 Ala Ala Thr Leu His Gly Arg Cys Trp Val Ala Lys Gly Ala Asp Ser

35

40

190

45

Ala Ala Leu Arg Gln Arg Gly Gly Gly Arg Cys Met His Ile Ala Asp  
50 55 60

Glu Lys Val Arg Gly Leu Ser Gly Cys Asp Gly Ser  
65 70 75

&lt;210&gt; 406

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 406

Leu Cys Arg Arg Ala Ala Leu Ser Ala Pro Phe Ala Thr Gln His Arg  
1 5 10 15

Pro Trp Ser Val Ala Ala Ala Cys Leu  
20 25

&lt;210&gt; 407

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 407

Arg Gly Phe Trp Trp Met Arg Gly Arg Gln Ala Ala Ala Thr Leu His  
1 5 10 15

Gly Arg Cys Trp Val Ala Lys Gly  
20

&lt;210&gt; 408

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 408

Gln Arg Gly Gly Gly Arg Cys Met His Ile Ala Asp Glu Lys Val Arg  
1 5 10 15

Gly Leu Ser Gly Cys Asp Gly  
20

&lt;210&gt; 409

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 409

Thr His Pro Ser His Pro Ser Ile Val Ile Gln Ser Thr Val Ser Leu  
1 5 10 15

Cys Leu Thr Ala Ser Ser Arg Arg Lys Lys Ser Asp Cys Leu Ser Leu

```
<210> 410
<211> 27
<212> PRT
<213> Homo sapiens
```

```

<400> 410
Val Ile Gln Ser Thr Val Ser Leu Cys Leu Thr Ala Ser Ser Arg Arg
  1                      5                      10                      15

Lys Lys Ser Asp Cys Leu Ser Leu Cys Gln Val
          20                      25

```

```
<210> 411
<211> 26
<212> PRT
<213> Homo sapiens
```

```

<400> 411
Ile Cys Lys Glu Ser Ser Leu Pro Cys Lys Glu Ile Gln Gly Lys Ala
  1                               10                          15
Cys Tyr Phe Cys His His Pro Ala Gln Gln
      20                25

```

```
<210> 412
<211> 188
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (140)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (149)
<223> Xaa equals any of the naturally occurring L-amino acids
```

&lt;400&gt; 412

(92)

Ser Leu Gln Val Leu Arg Thr Leu Gly Ser Lys Cys Gly Asp Phe Leu  
 1 5 10 15  
 Arg Ser Arg Phe Cys Lys Asp Val Leu Pro Lys Leu Ala Gly Ser Leu  
 20 25 30  
 Val Thr Gln Ala Pro Ile Ser Ala Arg Ala Gly Pro Val Tyr Ser His  
 35 40 45  
 Thr Leu Ala Phe Lys Leu Gln Leu Ala Val Leu Gln Gly Leu Gly Pro  
 50 55 60  
 Leu Cys Glu Arg Leu Asp Leu Gly Glu Gly Asp Leu Asn Lys Val Ala  
 65 70 75 80  
 Asp Ala Cys Leu Ile Tyr Leu Ser Val Lys Gln Pro Val Lys Leu Gln  
 85 90 95  
 Glu Ala Ala Arg Ser Val Phe Leu His Leu Met Lys Val Asp Pro Asp  
 100 105 110  
 Ser Thr Trp Phe Leu Leu Asn Glu Leu Tyr Cys Pro Val Gln Phe Thr  
 115 120 125  
 Pro Pro His Pro Ser Leu His Pro Val Gln Leu Xaa Gly Ala Ser Gly  
 130 135 140  
 Gln Gln Asn Pro Xaa His Asp Gln Arg Ala Pro Ala Ala Gln Gly Ala  
 145 150 155 160  
 Ala Val Thr Leu Leu Pro His His Arg Gly His Arg Ser Leu Pro Tyr  
 165 170 175  
 Cys Gln Pro Glu Ala Gly Leu Thr Pro Pro Arg Pro  
 180 185

&lt;210&gt; 413

&lt;211&gt; 138

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 413

Gly Ala Asp Gly Asn Val Ser Asp Phe Asp Asn Glu Glu Glu Glu Gln  
 1 5 10 15  
 Ser Val Pro Pro Lys Val Asp Glu Asn Asp Thr Arg Pro Asp Val Glu  
 20 25 30  
 Pro Pro Leu Pro Leu Gln Ile Gln Ile Ala Met Asp Val Met Glu Arg  
 35 40 45  
 Cys Ile His Leu Leu Ser Asp Lys Asn Leu Gln Ile Arg Leu Lys Val  
 50 55 60  
 Leu Asp Val Leu Asp Leu Cys Val Val Val Leu Gln Ser His Lys Asn

```
<210> 417
<211> 26
<212> PRT
<213> Homo sapiens
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194

&lt;400&gt; 417

Trp Pro Ser Leu Val His Arg Leu Thr Arg Asp Ala Pro Leu Ala Val  
 1 5 10 15

Leu Arg Ala Phe Lys Phe Tyr Val Pro Trp  
 20 25

&lt;210&gt; 418

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 418

Ser Leu Gly Ile Ser Thr Phe Gly Ile Met Val Phe Ser Val Tyr Phe  
 1 5 10 15

Gly Gly Ile Met Ile Ser Ile Pro Tyr Ser Gly Ile Ser Phe Gly Asn  
 20 25 30

Lys Lys Glu Leu Asn Ile Asp Ser Cys Tyr Asn Met Val Asn Leu Lys  
 35 40 45

Asn Ile Met Phe Ser Glu Arg Ser Gln Thr  
 50 55

&lt;210&gt; 419

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 419

His Ala Ser Gly Asn Asn Asp Pro Leu Trp Phe Leu Thr Tyr Leu  
 1 5 10 15

&lt;210&gt; 420

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 420

Met Val Phe Ser Val Tyr Phe Gly Gly Ile Met Ile Ser Ile Pro Tyr  
 1 5 10 15

Ser Gly Ile Ser Phe  
 20

&lt;210&gt; 421

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 421

Phe Gly Asn Lys Lys Glu Leu Asn Ile Asp Ser Cys Tyr Asn Met Val

1

5

145  
10

15

Asn Leu Lys Asn  
20

&lt;210&gt; 422

&lt;211&gt; 75

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (74)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 422

Met Asn Ser Phe Ser Val Ile Ala Ser Ile Val Val Leu Leu Pro Phe  
1 5 10 15

Pro Gly Leu Ser Val Ser Ala Cys Leu Pro Ser His Ser His Gln Cys  
20 25 30

Lys Thr Phe Ile Leu Leu Phe Leu Pro Ser Ser Glu Lys Thr Leu Xaa  
35 40 45

Xaa Xaa Pro Pro Ser His Ser Ser Thr Leu Gly Gly Gln Gly Gly Gln  
50 55 60

Ile Met Arg Ser Gly Asp Arg Xaa His Xaa Gly  
65 70 75

&lt;210&gt; 423

&lt;211&gt; 81

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

196

<220>  
 <221> SITE  
 <222> (5)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (60)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (74)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 423  
 Val Val Phe Phe Xaa Xaa Phe Phe Glu Met Glu Ser His Ser Val Ala  
   1                  5                  10                  15  
  
 Gln Ala Gly Val Gln Trp Arg Asn Leu Gly Ser Leu Gln Ala Leu Pro  
                   20                  25                  30  
  
 Pro Gly Phe Met Pro Phe Ser Cys Leu Ser Leu Pro Gly Ser Trp Asp  
           35                  40                  45  
  
 Tyr Arg Arg Pro Pro Pro Ser Pro Ala Asn Leu Xaa Cys Ile Phe Ser  
   50                  55                  60  
  
 Arg Asp Gly Gly His His Val Ser Gln Xaa Gly Leu Asp Leu Leu Thr  
   65                  70                  75                  80  
  
 Ser

<210> 424  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 424  
 Ile Val Val Leu Leu Pro Phe Pro Gly Leu Ser Val Ser Ala Cys Leu  
   1                  5                  10                  15  
  
 Pro Ser His Ser His Gln Cys Lys Thr Phe Ile Leu  
           20                  25

<210> 425  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 425

197

Pro Gly Phe Met Pro Phe Ser Cys Leu Ser Leu Pro Gly Ser Trp Asp  
 1 5 10 15

Tyr Arg Arg Pro Pro Pro Ser Pro Ala Asn  
 20 25

&lt;210&gt; 426

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 426

Tyr Arg Phe Lys Asn Pro Lys Cys Arg Leu Phe Ser Val Pro Cys Arg  
 1 5 10 15

&lt;210&gt; 427

&lt;211&gt; 128

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 427

Thr Gln Asn Arg Glu Leu Leu Ala Trp Lys Pro Lys Gly Thr Asp Asp  
 1 5 10 15

Ile Cys Thr Ser His Asn Thr Thr His Ile Gln Lys Met Pro Gly Glu  
 20 25 30

Ala Asn Ser Cys Cys Pro Arg Gly Ala Lys Ser Tyr His Ile Asp Cys  
 35 40 45

Trp Pro Pro Ala Leu Phe Pro Arg Cys Val Ala Tyr Leu Phe Leu Asn  
 50 55 60

Lys Pro Ala Thr Leu Arg Lys Lys Tyr Tyr Cys Lys Pro Tyr His Thr  
 65 70 75 80

Gln Leu His Pro Ala Trp His Arg Glu Lys Ser Ala Phe Trp Ile Phe  
 85 90 95

Glu Thr Val Ser Gln Ser Lys Gln Ser Leu Thr Ser Leu Val Tyr Ser  
 100 105 110

Val Asn Glu Leu Leu Val Leu Ser Asn Leu Ala Gln Trp Ala Leu Gly  
 115 120 125

&lt;210&gt; 428

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

(92)

&lt;400&gt; 428

Ala Trp Lys Pro Lys Gly Thr Asp Asp Ile Cys Thr Ser His Asn Thr  
 1 5 10 15

Thr His Ile Gln Lys Met Pro  
 20

&lt;210&gt; 429

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 429

Cys Pro Arg Gly Ala Lys Ser Tyr His Ile Asp Cys Trp Pro Pro Ala  
 1 5 10 15

Leu Phe Pro Arg Cys Val Ala Tyr Leu  
 20 25

&lt;210&gt; 430

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 430

Ser Tyr His Ile Asp Cys Trp Pro Pro Ala Leu Phe Pro Arg Cys Val  
 1 5 10 15

Ala Tyr Leu Phe Leu Asn Lys Pro Ala Thr  
 20 25

&lt;210&gt; 431

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 431

Arg Lys Lys Tyr Tyr Cys Lys Pro Tyr His Thr Gln Leu His Pro Ala  
 1 5 10 15

Trp His Arg Glu Lys Ser Ala Phe Trp Ile Phe Glu Thr  
 20 25

&lt;210&gt; 432

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 432

Ile Cys Leu Asp Ser Cys Ser Gln Val Ser Val Thr Ser Leu Trp Ser  
 1 5 10 15

Phe Leu Arg Val His Ser Leu Val Gln Thr<sup>199</sup> Leu Trp  
 20 25

<210> 433  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<400> 433  
 His Tyr Cys Cys Asp Phe Gly Thr Ser Leu Leu Gly Phe Tyr Val Pro  
 1 5 10 15

Phe His Tyr Tyr Val His Met Val Asn Ile Ile Leu Thr Thr Ile Asp  
 20 25 30

Phe Tyr His Tyr Lys Phe Cys Cys Ser Gln Asn Ala Asn Lys His Cys  
 35 40 45

Phe Lys His Phe Gln Ile Met Thr Thr Val Pro Tyr Leu Asn Ile Asn  
 50 55 60

Lys Glu Asn Leu Arg Phe Lys Asn Ile Phe Lys  
 65 70 75

<210> 434  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 434  
 Thr Ser Leu Leu Gly Phe Tyr Val Pro Phe His Tyr Tyr Val His Met  
 1 5 10 15

Val Asn Ile Ile Leu Thr Thr Ile Asp Phe Tyr  
 20 25

<210> 435  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 435  
 Phe Gln Ile Met Thr Thr Val Pro Tyr Leu Asn Ile Asn Lys Glu Asn  
 1 5 10 15

Leu Arg Phe Lys Asn Ile  
 20

<210> 436  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<400> 436

200

Ile	Ser	Glu	Ser	Met	Ser	Leu	Val	Arg	Ser	Leu	Gln	Phe	Tyr	Arg	Gly	1	5	10	15
Lys	Asn	Arg	Ala	Glu	Arg	Thr	Val	Ile	Ser	Ser	Ser	Ser	His	Ser	Cys	20	25	30	
His	Leu	Ile	Asp	Leu	Glu	Phe	Gln	Pro	Arg	Ser	Asp	Gly	Glu	Val	Ser	35	40	45	
Ile	Ser	Phe	Leu	Glu	Lys	Gly	Val	Glu	Leu	Arg	Trp	Gly	Met	Gly	Leu	50	55	60	
Glu	Asp	Leu	Ile	Gly	Leu	Gly	Leu	Gly	Val	Ser	Thr	Arg	Arg	Ser	Thr	65	70	75	80
Val	Arg	Arg	Lys	Glu	Pro	Thr	Lys	Ala	Gly	Met	His	Thr	Ala	Cys	Ser	85	90	95	
Glu	Glu	Met	Glu	Pro	Glu	Asn	Arg	Glu	Asn	100	105								

<210> 437  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<400> 437

Asp	Gly	Ser	Arg	Ser	Val	Ala	Gln	Ala	Arg	Val	Gln	Trp	His	His	Arg	1	5	10	15
Gly	Ser	Leu	Pro	Pro	Leu	Pro	Pro	Arg	Phe	Lys	Gln	Phe	Pro	Leu	Arg	20	25	30	
His	Leu	Arg	Val	Gly	Gly	Ile	Thr	Gly	Ala	Cys	Arg	His	Thr	Gln	Ile	35	40	45	
Ile	Phe	Val	Val	Leu	Val	Gln	Met	Gly	Phe	His	His	Val	Gly	Gln	Ala	50	55	60	
Gly	Leu	Glu	Leu	Leu	Thr	Ser	Gly	Asp	Pro	Pro	Ala	Leu	Ala	Ser	Gln	65	70	75	80
Ser	Ala	Gly	Ile	Thr	Gly	Val	Ser	His	Ser	Thr	Arg	Pro	Lys	Leu	Leu	85	90	95	
Ser	Trp	Leu	Pro	Ser	Asp	Asn	Leu	Leu	Gly	Met	Ala	Leu	Tyr	Ser	Ile	100	105	110	
Gln	Trp	Ala	Leu	Leu	Ala	Asn	Ser	Leu	Tyr	Phe	Gln	Val	Pro	Ser	Pro	115	120	125	
Leu	Ser	Met	Leu	Cys	Ala	Phe	Leu	Pro	Leu	Trp	Val	Pro	Ser	Ala	130	135	140		

<210> 438  
 <211> 27

&lt;212&gt; PRT

29

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

Arg	Gly	Lys	Asn	Arg	Ala	Glu	Arg	Thr	Val	Ile	Ser	Ser	Ser	Ser	His
1				5					10					15	

Ser	Cys	His	Leu	Ile	Asp	Leu	Glu	Phe	Gln	Pro
			20					25		

&lt;210&gt; 439

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 439

Leu	Gly	Leu	Gly	Val	Ser	Thr	Arg	Arg	Ser	Thr	Val	Arg	Arg	Lys	Glu
1				5					10					15	

Pro	Thr	Lys	Ala	Gly	Met	His	Thr	Ala	Cys	Ser	Glu	Glu	Met	Glu	Pro
			20					25					30		

&lt;210&gt; 440

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

Gly	Asp	Pro	Pro	Ala	Leu	Ala	Ser	Gln	Ser	Ala	Gly	Ile	Thr	Gly	Val
1				5				10						15	

Ser	His	Ser	Thr	Arg	Pro	Lys	Leu
			20				

&lt;210&gt; 441

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

Ala	Leu	Tyr	Ser	Ile	Gln	Trp	Ala	Leu	Leu	Ala	Asn	Ser	Leu	Tyr	Phe
1				5				10						15	

Gln	Val	Pro	Ser	Pro	Leu	Ser	Met	Leu
			20				25	

&lt;210&gt; 442

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

Asp Arg Ile Leu Leu Phe Tyr Ser Arg Asp Gly Gln Thr Thr Ser Lys  
 1 5 10 15

Gly Pro Asn Pro Ala Cys Cys Leu Phe Leu Leu Lys Lys Phe Tyr Trp  
 20 25 30

Asn Thr Ala  
 35

&lt;210&gt; 443

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 443

Asp Gly Gln Thr Thr Ser Lys Gly Pro Asn Pro Ala Cys Cys Leu Phe  
 1 5 10 15

Leu Leu Lys Lys Phe  
 20

&lt;210&gt; 444

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 444

Asp Pro Arg Val Arg Arg Thr Leu Asp Leu Gly Ile Thr Leu Tyr Leu  
 1 5 10 15

Phe Leu Tyr Ile Phe Leu Ser Leu  
 20

&lt;210&gt; 445

&lt;211&gt; 244

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 445

Pro Ala Leu Gly Glu Cys Cys Leu Asp Ala Phe Leu Phe Leu Leu Gly  
 1 5 10 15

Lys Gln Leu Lys Lys Ser Gly Glu Lys Pro Leu Leu Gly Gly Ser Leu  
 20 25 30

Met Glu Tyr Ala Ile Leu Ser Ala Ile Ala Ala Met Asn Glu Pro Lys  
 35 40 45

Thr Cys Ser Thr Thr Ala Leu Lys Lys Tyr Val Leu Glu Asn His Pro  
 50 55 60

Gly Thr Asn Ser Asn Tyr Gln Met His Leu Leu Lys Lys Thr Leu Gln  
 65 70 75 80

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<210> 446
<211> 152
<212> PRT
<213> Homo sapiens
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<400> 446

Asp	Phe	Glu	Phe	His	His	Asp	Thr	Leu	Phe	Ser	Tyr	Lys	Ile	Tyr	Phe
1				5					10					15	
Phe	Thr	Leu	Lys	Asp	Phe	Phe	Met	Val	Asp	Leu	Pro	Leu	Pro	Gly	Asn
			20					25					30		
Phe	Thr	Ser	Phe	Leu	Ala	Leu	Val	Ala	Gly	Phe	Phe	Glu	Glu	Pro	Pro
		35					40					45			
Leu	Gly	Phe	Leu	Met	Thr	Val	Asp	Glu	Gly	Leu	Val	Phe	Leu	Ala	Gly
	50					55					60				
Val	Leu	Ala	Leu	Gly	Gly	Ala	Phe	Leu	Gly	Lys	Gly	Leu	Ala	Phe	Pro
65					70					75					80
Arg	Trp	Ala	Ala	Glu	Thr	Leu	Gly	Ala	Gly	Leu	Asp	Pro	Leu	Cys	Phe
				85					90					95	

304

Thr	Asp	Ala	Ala	Phe	Pro	Gly	Asp	Leu	Ala	Gly	Val	Phe	Phe	Cys	Asn
		100						105					110		
Leu	Leu	Leu	Gly	Gly	Gly	Ser	Ser	Ser	Ser	Glu	Ser	Ser	Ser	Asp	Asp
		115					120					125			
Ser	Ser	Ser	Ser	Ser	Ser	Ser	Ser	Leu	Glu	Ser	Ser	Gly	Ser	Phe	Phe
	130						135				140				
Gly	Asn	Arg	Thr	Pro	Gly	Leu	Gly								
145					150										

<210> 447  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 447  

Cys	Leu	Asp	Ala	Phe	Leu	Phe	Leu	Leu	Gly	Lys	Gln	Leu	Lys	Lys	Ser
1				5					10					15	

Gly	Glu	Lys	Pro	Leu	Leu	Gly	Gly	Ser	Leu	Met	Glu				
			20					25							

<210> 448  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 448  

Tyr	Gln	Met	His	Leu	Leu	Lys	Lys	Thr	Leu	Gln	Lys	Cys	Glu	Lys	Asn
1				5				10						15	

Gly	Trp	Met	Glu	Gln	Ile	Ser	Gly	Lys	Gly	Phe	Ser	Gly	Thr		
			20					25					30		

<210> 449  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 449  

Lys	Thr	Pro	Ala	Lys	Ser	Pro	Gly	Lys	Ala	Ala	Ser	Val	Lys	Gln	Arg
1				5				10						15	

Gly	Ser	Lys	Pro	Ala	Pro	Lys	Val	Ser	Ala	Ala	Gln				
			20					25							

<210> 450  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 450

285

Ser	Ser	Lys	Lys	Pro	Ala	Thr	Ser	Ala	Arg	Lys	Glu	Val	Lys	Leu	Pro
1				5					10					15	

Gly	Lys	Gly	Lys	Ser	Thr	Met	Lys	Lys	Ser	Phe	Arg
			20					25			

<210> 451  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

Val	Asp	Glu	Gly	Leu	Val	Phe	Leu	Ala	Gly	Val	Leu	Ala	Leu	Gly	Gly
1				5					10					15	

Ala	Phe	Leu	Gly	Lys	Gly	Leu
			20			

<210> 452  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

Gly	Leu	Asp	Pro	Leu	Cys	Phe	Thr	Asp	Ala	Ala	Phe	Pro	Gly	Asp	Leu
1				5					10					15	

Ala	Gly	Val	Phe	Phe	Cys	Asn	Leu	Leu
			20				25	

<210> 453  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

Thr	Met	Leu	Phe	Tyr	Leu	Ser	Ser	Gln	Pro	Asp	Trp	Gln	Leu	Asp	Phe
1				5					10					15	

Phe	Arg	Val	Ser	Phe	Asn	Gly	Pro	Val	Phe	Phe	Ile	Ile	Ile	Phe	Asn
			20				25						30		

Asp	Arg	Ala	Gly	Phe	Arg	Met	Gln	Ala	Leu	Val	Ser	Gln	Ala	Ala	Cys
		35					40					45			

Arg	Arg	Ser	Arg	Tyr	Lys	Leu	Ser	Val	Val	Tyr
		50				55				

<210> 454  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 454

Asp Arg Ala Gly Phe Arg Met Gln Ala Leu Val Ser Gln Ala Ala Cys  
1 5 10 15

Arg Arg Ser Arg Tyr Lys Leu  
20

<210> 455

<211> 22

<212> PRT

<213> Homo sapiens

<400> 455

Leu Ala Ala Gly Ile Leu Asn Ser Ser Leu Pro Ala Leu Tyr His Ser  
1 5 10 15

Val Glu Glu Ile Ser Gln  
20

<210> 456

<211> 45

<212> PRT

<213> Homo sapiens

<400> 456

Xaa Tyr Arg Met Asn Thr Lys Phe Leu Glu Ser Tyr Lys Met Ser Thr  
1 5 10 15

Thr Leu Ser Arg Arg His Gln Asn Val Ser Leu Cys Lys Asp Met Lys  
20 25 30

Thr Pro Ala Gly Thr Asp Thr Lys Ile Ala Phe Leu Glu  
35 40 45

<210> 457

<211> 21

<212> PRT

<213> Homo sapiens

<400> 457

Ser Tyr Lys Met Ser Thr Thr Leu Ser Arg Arg His Gln Asn Val Ser  
1 5 10 15

Leu Cys Lys Asp Met  
20

<210> 458

<211> 57

<212> PRT

<213> Homo sapiens

<400> 458

Ile Cys Ile Glu Ser Leu Met Leu His Tyr Ile Ala Leu Val Phe Glu  
1 5 10 15

107

Met Ala Phe Met Phe Pro Leu Val Tyr His Glu Met Gly Ser Asp Ser  
                   20                  25                  30

Ile Arg Phe His Leu Cys Gln Val Asp Ser Cys Leu Pro Ser Met Met  
           35                  40                  45

Arg Phe Phe Phe Ser Phe Pro Phe Leu  
       50                  55

&lt;210&gt; 459

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 459

Tyr Ile Ala Leu Val Phe Glu Met Ala Phe Met Phe Pro Leu Val Tyr  
       1                  5                  10                  15

His Glu Met Gly Ser  
                   20

&lt;210&gt; 460

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 460

Ser Asp Ser Ile Arg Phe His Leu Cys Gln Val Asp Ser Cys Leu Pro  
       1                  5                  10                  15

Ser Met Met Arg Phe  
                   20

&lt;210&gt; 461

&lt;211&gt; 115

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 461

Gly Gly Val Ser Val Gln Asp Gly Ser Leu Arg Glu Glu Thr Asp Val  
       1                  5                  10                  15

Gly Glu Gly Gly Arg Pro Arg Gly Gly Gln Ser Glu Gly Ala Arg Val  
           20                  25                  30

Thr Arg Arg Pro Ser Pro Pro Asp Ser Asn Ala Ser Ala Phe Asp Leu  
           35                  40                  45

Asp Leu Asp Phe Ser Pro Phe Cys Ile Trp Cys Tyr Arg Leu Glu Thr  
       50                  55                  60

Pro Ala Glu Val Val Phe Ser Pro Ala Pro Leu Arg Leu Ser Gly Pro  
       65                  70                  75                  80

Gly Leu Ala Pro Val Val Phe Val Ser Thr Leu Pro Ser Leu Gln Pro

85

208  
90

95

Ser Ser Phe Cys Gly Trp Asp Leu Pro Ala Arg Pro Arg Gly Leu Ser  
 100 105 110

Gly Phe Arg  
 115

&lt;210&gt; 462

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 462

Phe Thr Asn Lys Ser Cys Ser Lys Met Ser Ser Thr His Leu Tyr Lys  
 1 5 10 15

Gly Ser Asp Val Leu Cys Tyr Ala Arg Ser Ser Glu Ser Met Ser Leu  
 20 25 30

Ser Cys Gly Asp Val Ala Asn Ala Gly Arg Leu Thr Pro Arg Leu His  
 35 40 45

Leu Ala Arg Ser Ala Ser Gln Gly Pro Pro Thr Leu Pro Arg Val Pro  
 50 55 60

Pro Arg Gly Ser Arg Pro Pro Thr Ala Gly Glu Ser Pro Ala Pro Arg  
 65 70 75 80

Thr Xaa Ser Leu Glu Asn His Lys Asn Ile Asp His Leu Ser Ser Asn  
 85 90 95

Ser His Gly Lys Phe Arg Ile Tyr Gly Gln Asn Asp Ile Lys Ile  
 100 105 110

&lt;210&gt; 463

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 463

Gln Asp Val Ile Tyr Thr Phe Val Gln Arg Phe Arg Arg Pro Met Leu  
 1 5 10 15

Cys Thr Ile Leu Arg Lys Tyr Glu Pro Val Val Arg Gly Arg Arg Lys  
 20 25 30

Arg Trp Gln Ala His Pro Ser Ser Ala Phe Gly Lys Lys Arg Leu Pro  
 35 40 45

Arg Pro Pro His Pro Ala Gln Gly Ala Pro Gln Arg Glu Gln Ala Ser

50 55 59 60  
His Ser Trp Arg Glu Pro Gly Pro Gln Asn Thr Phe Pro Arg Lys Pro  
65 70 75 80

<210> 464  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 464  
Arg Glu Glu Thr Asp Val Gly Glu Gly Gly Arg Pro Arg Gly Gly Gln  
1 5 10 15

Ser Glu Gly Ala Arg Val  
20

<210> 465  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 465  
Gly Pro Gly Leu Ala Pro Val Val Phe Val Ser Thr Leu Pro Ser Leu  
1 5 10 15

Gln Pro Ser Ser Phe Cys Gly Trp Asp Leu Pro  
20 25

<210> 466  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 466  
Met Ser Ser Thr His Leu Tyr Lys Gly Ser Asp Val Leu Cys Tyr Ala  
1 5 10 15

Arg Ser Ser Glu Ser Met Ser Leu  
20

<210> 467  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 467  
Ser Gln Gly Pro Pro Thr Leu Pro Arg Val Pro Pro Arg Gly Ser Arg  
1 5 10 15

Pro Pro Thr Ala Gly Glu Ser Pro Ala Pro Arg Thr

20 25 710

<210> 468  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 468  
 Arg Phe Arg Arg Pro Met Leu Cys Thr Ile Leu Arg Lys Tyr Glu Pro  
 1 5 10 15

Val Val Arg Gly Arg Arg Lys Arg Trp  
 20 25

<210> 469  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 469  
 Arg Leu Pro Arg Pro Pro His Pro Ala Gln Gly Ala Pro Gln Arg Glu  
 1 5 10 15

Gln Ala Ser His Ser Trp Arg Glu  
 20

<210> 470  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 470  
 Arg Gly Met Arg Gly Arg Trp Leu Val Ser Ser Gly Ala Ala Phe Pro  
 1 5 10 15

Ile Pro Leu Asn Gly Phe Cys Glu Ser Arg Glu Phe Phe Pro Asp Ser  
 20 25 30

Gly Ser Val Leu Leu His Trp Arg Pro Asn Xaa Val Leu Ile Glu Ile  
 35 40 45

Lys Val Phe Gly Ser Arg Ser Gln Ser Leu Ile Ser Ser Lys Asn Leu  
 50 55 60

Lys Thr Ser Leu Thr Phe Ile Tyr Gly Lys Val Glu Glu Val Leu Asn  
 65 70 75 80

Asn

<210> 471  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 471  
 Leu Lys Leu Ser Ser Ala Asp Ser Gln Ala Ile Met Asn Ile Phe Ser  
   1                  5                  10                  15  
 Ala Asp Cys Met Pro Arg Leu His Ile Ala Leu Gln Thr Glu Met Ile  
                   20                  25                  30  
 Pro Asn Arg Ala Pro Gln Gly Gly Ala Ala Ala Asn Leu Trp His Glu  
                   35                  40                  45  
 Ala Gln Tyr Arg Arg Leu Pro Phe Ser Arg Ala Pro Glu Xaa Thr Asp  
   50                  55                  60  
 Ala His Gln Ala Ser Ala Gln Arg Gly Ala Ala Gln Leu Pro Arg Glu  
   65                  70                  75                  80  
 Gln

<210> 472  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (28)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 472  
 Pro Ile Pro Leu Asn Gly Phe Cys Glu Ser Arg Glu Phe Phe Pro Asp  
   1                  5                  10                  15  
 Ser Gly Ser Val Leu Leu His Trp Arg Pro Asn Xaa  
                   20                  25

<210> 473  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 473  
 Asn Ile Phe Ser Ala Asp Cys Met Pro Arg Leu His Ile Ala Leu Gln  
   1                  5                  10                  15

312

Thr Glu Met Ile Pro Asn Arg Ala Pro Gln Gly Gly Ala  
                   20                                  25

&lt;210&gt; 474

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

Thr Phe Arg Leu Val Ser Ala His Leu Lys Thr Arg Lys Leu Ile Asn  
       1                                  5                                  10                                  15

Pro Glu Ala Ala Glu Arg Arg Trp Arg Asp Trp Asp Ser Arg Gln Gly  
                   20                                  25                                  30

Trp Leu Ser Val Lys  
                   35

&lt;210&gt; 475

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 475

Lys Thr Arg Lys Leu Ile Asn Pro Glu Ala Ala Glu Arg Arg Trp Arg  
       1                                  5                                  10                                  15

Asp Trp Asp Ser Arg  
                   20

&lt;210&gt; 476

&lt;211&gt; 83

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 476

Trp Asn Tyr Thr Val Asn Asn Leu Tyr Leu Phe Ser Phe Ser Ile Val  
       1                                  5                                  10                                  15

Ser Met Lys Phe Met His Val Leu Ser Ile Asn Ile Phe Phe Gly Arg  
                   20                                  25                                  30

Ala Arg Trp Leu Thr Pro Val Ile Pro Ala Leu Leu Glu Ala Glu Ala  
                   35                                  40                                  45

Gly Gly Ser Leu Gly Gln Glu Phe Lys Thr Ser Leu Gly Lys Asp Gly  
           50                                  55                                  60

Glu Thr Pro Ser Leu Leu Lys Ile Gln Lys Leu Ala Gly His Gly Gly  
       65                                  70                                  75                                  80

Arg Arg Leu

<210> 477  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

712

<400> 477  
 Asp Gln Pro Gly Lys His Gly Glu Thr Leu Ser Leu Leu Lys Met Gln  
     1                    5                    10                    15  
 Lys Leu Thr Trp Cys Gly Gly Met Pro Phe Val Ile Pro Ser Tyr Ser  
                     20                    25                    30  
 Arg Ser Pro Arg Pro Glu Asn Arg Leu Asn Leu Gly Asp Arg Gly Cys  
                     35                    40                    45  
 Thr Glu Leu Leu His Ser Ser Leu Gly Asn Arg Val Arg Leu Ser Lys  
                     50                    55                    60  
 Lys Lys Glu Val Tyr Met Met Glu Leu Tyr Ser Lys  
     65                    70                    75

<210> 478  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 478  
 Val Ile Pro Ala Leu Leu Glu Ala Glu Ala Gly Gly Ser Leu Gly Gln  
     1                    5                    10                    15  
 Glu Phe Lys Thr Ser Leu Gly Lys Asp Gly Glu Thr  
                     20                    25

<210> 479  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 479  
 Asn Arg Leu Asn Leu Gly Asp Arg Gly Cys Thr Glu Leu Leu His Ser  
     1                    5                    10                    15  
 Ser Leu Gly Asn Arg Val Arg Leu Ser Lys Lys Lys Glu  
                     20                    25

<210> 480  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 480  
 His Ala Ser Glu His Leu Ala Ala Leu Pro Val Asn Val Lys Ile Gly  
     1                    5                    10                    15

Lys

214

<210> 481  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 481  
 Leu Val Cys Ile Leu Leu Val His Trp Ile Pro Pro Leu Gly Ala Trp  
     1                    5                    10                    15  
 Gly Leu Ser Leu Met Leu Phe Leu Ile Leu Glu Gln Arg Cys Gly Lys  
                     20                    25                    30  
 Gly Lys Trp Arg Asn Ala Leu Leu Ser Val Ser Phe Ser Val Pro Gln  
                     35                    40                    45  
 Leu Gln Met Gln Lys Val Ser Leu Asp Ser Thr Pro Leu Asn Val Asn  
                     50                    55                    60  
 His Asp Lys Met Asp Ile Trp Lys Leu Thr Pro Lys Leu  
                     65                    70                    75

<210> 482  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 482  
 Ile Met Ile Lys Trp Ile Phe Gly Asn Leu Leu Leu Ser Cys Asp Leu  
     1                    5                    10                    15  
 Gly Cys Ile Ser Thr Ser Gly Leu Pro Gln Tyr Gln Gly Leu Arg Leu  
                     20                    25                    30  
 Leu Asn Phe Glu Tyr Ser Leu Gly Phe Met Leu Arg Ser Leu Trp Ser  
                     35                    40                    45  
 Arg Ser Ala Ile Gln Cys Phe Phe Ser  
                     50                    55

<210> 483  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 483  
 Leu Leu Leu Ser Cys Asp Leu Gly Cys Ile Ser Thr Ser Gly Leu Pro  
     1                    5                    10                    15  
 Gln Tyr Gln Gly Leu  
                     20

<210> 484

<211> 21  
 <212> PRT  
 <213> Homo sapiens

HS

<400> 484  
 Leu Arg Leu Leu Asn Phe Glu Tyr Ser Leu Gly Phe Met Leu Arg Ser  
     1                    5                    10                    15  
 Leu Trp Ser Arg Ser  
                     20

<210> 485  
 <211> 78  
 <212> PRT  
 <213> Homo sapiens

<400> 485  
 Ala Ser Pro His Leu Phe Ile Glu Lys Trp Gly Arg Ala Phe Ile Leu  
     1                    5                    10                    15  
 Arg Lys Leu Leu Leu Val Pro Val Ile Ser Lys Arg Ile Ile Asn Ile  
                     20                    25                    30  
 Met Ala His Gln Val Lys Pro Pro Ile Phe Cys Ala Met Ile Met Cys  
                     35                    40                    45  
 Asn Leu Phe Cys Ser Gly Tyr Glu His Leu Leu Phe Thr Leu Met Arg  
     50                    55                    60  
 Phe Phe Ser Phe Glu Gln Ile Phe Asp Glu Val Val Phe His  
     65                    70                    75

<210> 486  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 486  
 Lys Leu Leu Leu Val Pro Val Ile Ser Lys Arg Ile Ile Asn Ile Met  
     1                    5                    10                    15  
 Ala His Gln Val Lys Pro Pro Ile Phe  
                     20                    25

<210> 487  
 <211> 358  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (352)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>

&lt;221&gt; SITE

26

&lt;222&gt; (356)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 487

Phe	Ala	Val	Ile	Arg	Phe	Glu	Ser	Ile	Ile	His	Glu	Phe	Asp	Pro	Trp
1				5					10					15	

Phe	Asn	Tyr	Arg	Ser	Thr	His	His	Leu	Ala	Ser	His	Gly	Phe	Tyr	Glu
			20					25					30		

Phe	Leu	Asn	Trp	Phe	Asp	Glu	Arg	Ala	Trp	Tyr	Pro	Leu	Gly	Arg	Ile
		35					40						45		

Val	Gly	Gly	Thr	Val	Tyr	Pro	Gly	Leu	Met	Ile	Thr	Ala	Gly	Leu	Ile
	50						55					60			

His	Trp	Ile	Leu	Asn	Thr	Leu	Asn	Ile	Thr	Val	His	Ile	Arg	Asp	Val
65					70					75					80

Cys	Val	Phe	Leu	Ala	Pro	Thr	Phe	Ser	Gly	Leu	Thr	Ser	Ile	Ser	Thr
				85					90					95	

Phe	Leu	Leu	Thr	Arg	Glu	Leu	Trp	Asn	Gln	Gly	Ala	Gly	Leu	Leu	Ala
			100					105					110		

Ala	Cys	Phe	Ile	Ala	Ile	Val	Pro	Gly	Tyr	Ile	Ser	Arg	Ser	Val	Ala
		115					120					125			

Gly	Ser	Phe	Asp	Asn	Glu	Gly	Ile	Ala	Ile	Phe	Ala	Leu	Gln	Phe	Thr
	130					135					140				

Tyr	Tyr	Leu	Trp	Val	Lys	Ser	Val	Lys	Thr	Gly	Ser	Val	Phe	Trp	Thr
145					150					155					160

Met	Cys	Cys	Cys	Leu	Ser	Tyr	Phe	Tyr	Met	Val	Ser	Ala	Trp	Gly	Gly
				165					170					175	

Tyr	Val	Phe	Ile	Ile	Asn	Leu	Ile	Pro	Leu	His	Val	Phe	Val	Leu	Leu
			180					185					190		

Leu	Met	Gln	Arg	Tyr	Ser	Lys	Arg	Val	Tyr	Ile	Ala	Tyr	Ser	Thr	Phe
		195					200					205			

Tyr	Ile	Val	Gly	Leu	Ile	Leu	Ser	Met	Gln	Ile	Pro	Phe	Val	Gly	Phe
	210					215					220				

Gln	Pro	Ile	Arg	Thr	Ser	Glu	His	Met	Ala	Ala	Ala	Gly	Val	Phe	Ala
225					230					235					240

Leu	Leu	Gln	Ala	Tyr	Ala	Phe	Leu	Gln	Tyr	Leu	Arg	Asp	Arg	Leu	Thr
				245					250					255	

Lys	Gln	Glu	Phe	Gln	Thr	Leu	Phe	Phe	Leu	Gly	Val	Ser	Leu	Ala	Ala
			260					265					270		

Gly	Ala	Val	Phe	Leu	Ser	Val	Ile	Tyr	Leu	Thr	Tyr	Thr	Gly	Tyr	Ile
		275					280						285		

217

Ala Pro Trp Ser Gly Arg Phe Tyr Ser Leu Trp Asp Thr Gly Tyr Ala  
 290 295 300

Lys Ile His Ile Pro Ile Ile Ala Ser Val Ser Glu His Gln Pro Thr  
 305 310 315 320

Thr Trp Val Ser Phe Phe Phe Asp Leu His Ile Leu Val Cys Thr Phe  
 325 330 335

Pro Ala Gly Leu Trp Phe Cys Ile Lys Asn Ile Asn Asp Glu Arg Xaa  
 340 345 350

Phe Gly Lys Xaa Gly Phe  
 355

&lt;210&gt; 488

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 488

Glu Phe Asp Pro Trp Phe Asn Tyr Arg Ser Thr His His Leu Ala Ser  
 1 5 10 15

His Gly Phe Tyr Glu Phe Leu Asn Trp Phe Asp  
 20 25

&lt;210&gt; 489

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 489

Thr Arg Glu Leu Trp Asn Gln Gly Ala Gly Leu Leu Ala Ala Cys Phe  
 1 5 10 15

Ile Ala Ile Val Pro Gly Tyr  
 20

&lt;210&gt; 490

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 490

Thr Tyr Tyr Leu Trp Val Lys Ser Val Lys Thr Gly Ser Val Phe Trp  
 1 5 10 15

Thr Met Cys Cys Cys Leu  
 20

&lt;210&gt; 491

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

218

&lt;400&gt; 491

Gly Val Phe Ala Leu Leu Gln Ala Tyr Ala Phe Leu Gln Tyr Leu Arg  
 1 5 10 15

Asp Arg Leu Thr Lys Gln Glu Phe Gln  
 20 25

&lt;210&gt; 492

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 492

Tyr Ser Leu Trp Asp Thr Gly Tyr Ala Lys Ile His Ile Pro Ile Ile  
 1 5 10 15

Ala Ser Val Ser Glu His Gln Pro Thr Thr Trp  
 20 25

&lt;210&gt; 493

&lt;211&gt; 408

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (20)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 493

Met Gly His Met Leu Tyr Leu Leu Gly Asn Ile Asn Lys Arg Thr Met  
 1 5 10 15

His Lys Tyr Xaa Gln Glu Ser Lys Lys Ala Gly Lys Ala Ser Phe Ala  
 20 25 30

Tyr Ala Trp Val Leu Asp Glu Thr Gly Glu Glu Arg Glu Arg Gly Val  
 35 40 45

Thr Met Asp Val Gly Met Thr Lys Phe Glu Thr Thr Thr Lys Val Ile  
 50 55 60

Thr Leu Met Asp Ala Pro Gly His Lys Asp Phe Ile Pro Asn Met Ile  
 65 70 75 80

Thr Gly Ala Ala Gln Ala Asp Val Ala Val Leu Val Val Asp Ala Ser  
 85 90 95

Arg Gly Glu Phe Glu Ala Gly Phe Glu Thr Gly Gly Gln Thr Arg Glu  
 100 105 110

His Gly Leu Leu Val Arg Ser Leu Gly Val Thr Gln Leu Ala Val Ala  
 115 120 125

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Val Asn Lys Met Asp Gln Val Asn Trp Gln Gln Glu Arg Phe Gln Glu  
 130 135 140  
 Ile Thr Gly Lys Leu Gly His Phe Leu Lys Gln Ala Gly Phe Lys Glu  
 145 150 155 160  
 Ser Asp Val Gly Phe Ile Pro Thr Ser Gly Leu Ser Gly Glu Asn Leu  
 165 170 175  
 Ile Thr Arg Ser Gln Ser Ser Glu Leu Thr Lys Trp Tyr Lys Gly Leu  
 180 185 190  
 Cys Leu Leu Glu Gln Ile Asp Ser Phe Lys Pro Pro Gln Arg Ser Ile  
 195 200 205  
 Asp Lys Pro Phe Arg Leu Cys Val Ser Asp Val Phe Lys Asp Gln Gly  
 210 215 220  
 Ser Gly Phe Cys Ile Thr Gly Lys Ile Glu Ala Gly Tyr Ile Gln Thr  
 225 230 235 240  
 Gly Asp Arg Leu Leu Ala Met Pro Pro Asn Glu Thr Cys Thr Val Lys  
 245 250 255  
 Gly Ile Thr Leu His Asp Glu Pro Val Asp Trp Ala Ala Ala Gly Asp  
 260 265 270  
 His Val Ser Leu Thr Leu Val Gly Met Asp Ile Ile Lys Ile Asn Val  
 275 280 285  
 Gly Cys Ile Phe Cys Gly Pro Lys Val Pro Ile Lys Ala Cys Thr Arg  
 290 295 300  
 Phe Arg Ala Arg Ile Leu Ile Phe Asn Ile Glu Ile Pro Ile Thr Lys  
 305 310 315 320  
 Gly Phe Pro Val Leu Leu His Tyr Gln Thr Val Ser Glu Pro Ala Val  
 325 330 335  
 Ile Lys Arg Leu Ile Ser Val Leu Asn Lys Ser Thr Gly Glu Val Thr  
 340 345 350  
 Lys Lys Lys Pro Lys Phe Leu Thr Lys Gly Gln Asn Ala Leu Val Glu  
 355 360 365  
 Leu Gln Thr Gln Arg Pro Ile Ala Leu Glu Leu Tyr Lys Asp Phe Lys  
 370 375 380  
 Glu Leu Gly Arg Phe Met Leu Arg Tyr Gly Gly Ser Thr Ile Ala Ala  
 385 390 395 400  
 Gly Val Val Thr Glu Ile Lys Glu  
 405

&lt;210&gt; 494

&lt;211&gt; 21

<212> PRT  
<213> Homo sapiens

270

<220>  
<221> SITE  
<222> (16)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 494  
Leu Tyr Leu Leu Gly Asn Ile Asn Lys Arg Thr Met His Lys Tyr Xaa  
1 5 10 15

Gln Glu Ser Lys Lys  
20

<210> 495  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 495  
Leu Asp Glu Thr Gly Glu Glu Arg Glu Arg Gly Val Thr Met Asp Val  
1 5 10 15

Gly Met Thr Lys Phe Glu Thr  
20

<210> 496  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 496  
Gly His Lys Asp Phe Ile Pro Asn Met Ile Thr Gly Ala Ala Gln Ala  
1 5 10 15

Asp Val Ala Val Leu Val  
20

<210> 497  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 497  
Gly Phe Glu Thr Gly Gly Gln Thr Arg Glu His Gly Leu Leu Val Arg  
1 5 10 15

Ser Leu Gly Val Thr Gln Leu  
20

<210> 498  
<211> 23  
<212> PRT

&lt;213&gt; Homo sapiens

221

&lt;400&gt; 498

Trp Gln Gln Glu Arg Phe Gln Glu Ile Thr Gly Lys Leu Gly His Phe  
1 5 10 15

Leu Lys Gln Ala Gly Phe Lys  
20

&lt;210&gt; 499

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 499

Thr Ser Gly Leu Ser Gly Glu Asn Leu Ile Thr Arg Ser Gln Ser Ser  
1 5 10 15

Glu Leu Thr Lys Trp Tyr  
20

&lt;210&gt; 500

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 500

Pro Gln Arg Ser Ile Asp Lys Pro Phe Arg Leu Cys Val Ser Asp Val  
1 5 10 15

Phe Lys Asp Gln Gly Ser Gly  
20

&lt;210&gt; 501

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 501

Leu Ile Ser Val Leu Asn Lys Ser Thr Gly Glu Val Thr Lys Lys Lys  
1 5 10 15

Pro Lys Phe Leu Thr Lys  
20

&lt;210&gt; 502

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 502

Gln Arg Pro Ile Ala Leu Glu Leu Tyr Lys Asp Phe Lys Glu Leu Gly  
1 5 10 15

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Arg Phe Met Leu Arg Tyr Gly Gly Ser  
20 25

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# INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>183</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection ("ATCC")</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>16 OCTOBER 1997</u>	Accession Number <u>209368</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	


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# INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>183</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution <b>American Type Culture Collection ("ATCC")</b>	
Address of depositary institution <i>(including postal code and country)</i> <b>10801 University Boulevard  Manassas, Virginia 20110-2209  United States of America</b>	
Date of deposit  <b>23 OCTOBER 1997</b>	Accession Number  <b>209407</b>
<b>C. ADDITIONAL INDICATIONS</b> <i>(leave blank if not applicable)</i> This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> <i>(if the indications are not for all designated States)</i>	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> <i>(leave blank if not applicable)</i>	
The indications listed below will be submitted to the International Bureau later <i>(specify the general nature of the indications e.g., "Accession Number of Deposit")</i>	

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# INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>183</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection ("ATCC")</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>30 OCTOBER 1997</u>	Accession Number <u>209423</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/23435

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5, 23.1; 435/320.1, 440, 252.3, 69.1, 7.1; 530/350, 387.1; 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAPPERSTEIN, S.K. et al, p115 is a general vesicular transport factor related to the yeast endoplasmic reticulum to Golgi transport factor Usolp. Proceedings of the National Academy of Sciences USA. 17 January 1995, Vol. 92, No. 2, pages 522-526, see entire document.	1, 2, 5, and 7-10
X	BARROSO et al, Transcytosis-associated protein (TAP)/p115 is a general fusion factor required for binding of vesicles to acceptor membranes. Proceedings of the National Academy of Sciences USA. 17 January 1995, Vol. 92, No. 2, pages 527-531, see entire document.	11-13 and 16

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 JANUARY 1999

Date of mailing of the international search report

25 FEB 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
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Washington, D.C. 20231

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Authorized officer

JAMES MARTINELL

Telephone No. (703) 308-0196

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/23435

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	SOHADA et al, Phosphorylation of the vesicle docking protein p115 regulates its association with the Golgi membrane. Journal of Biological Chemistry. 27 February 1998, Vol. 273, No. 9, pages 5385-5388, see entire document.	1, 2, 5-13, and 16
A	ADAMS et al, complementary DNA sequencing: Expressed sequence tags and the human genome project. Science. 21 June 1991, Vol. 252, pages 1651-1656, see entire document.	1-22

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/23435

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 23  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claim 23 is directed to a product of the process of claim 20. Claim 20 is not a process for the production of a product, but a process for the detection of a substance. Hence, no meaningful search can be carried out.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/23435

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

G01N 33/68, 33/53; C07K 16/00; C12N 15/11, 15/12, 15/00, 15/63; A61K 38/17, 38/16; C12P 21/02

## A. CLASSIFICATION OF SUBJECT MATTER: US CL :

536/23.5, 23.1; 435/320.1, 440, 252.3, 69.1, 7.1; 530/350, 387.1; 514/12

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, MPSRCH (SEQ ID NOs 11 and 136 only). One nucleotide sequence and one amino acid sequence have been searched. It is not clear which sequences are embraced by the claims because the claims refer to sequences X and Y. The table beginning at page 183 contains many sequences X and Y, yet the claims refer to X and Y in the singular. If the claims are to embrace more than one X and more than one Y, it is not clear whether each X always requires the corresponding sequence Y. Additionally, the claims are in improper format in referring to the description (see PCT Rule 6.2(a)). Accordingly, the first X nucleotide sequence disclosed and the first Y amino acid sequence corresponding to the first X sequence disclosed in the table were searched.